

THE BEHAVIOURAL, COGNITIVE, AND NEURAL CORRELATES OF BLUNTED
PHYSIOLOGICAL REACTIONS TO ACUTE PSYCHOLOGICAL STRESS.

By

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Abstract

The overarching aim of this thesis was to better understand the behavioural, cognitive, and neural corollaries of blunted cardiovascular and/or cortisol reactions to acute psychological stress. As such, it was also concerned to further test the proposition that blunted cardiovascular and cortisol reactions to acute psychological stress are markers of an unconscious dysfunction in the motivational areas of the brain. These aims were achieved by using a mixed methods interdisciplinary approach encompassing both laboratory stress studies and secondary analyses of epidemiological datasets. Chapter 2 adduced evidence that blunted cardiovascular and cortisol reactivity was associated with a non-substance addiction, namely exercise dependence. Chapter 3 demonstrated that blunted cardiovascular and cortisol reactivity was related to disordered eating behaviour. Differences in stress reactivity between healthy controls and exercise dependent individuals or disordered eaters could not be explained by actual stress task performance, how engaged or how stressful participants found the stress task, cardio-respiratory fitness, and a number of other potential confounders. Chapters 4, 5, and 6 demonstrated that poor cognitive ability was associated with blunted stress reactivity retrospectively, cross-sectionally, and prospectively. Additionally, Chapter 6 demonstrated that blunted cardiac reactivity predicted cognitive decline over a 7 year period. Chapter 7 revealed brain activation differences between pre-determined exaggerated and blunted cardiac stress reactors during an acute stress exposure in a fMRI paradigm. Blunted cardiac reactors showed hypo-activation in the areas of the brain associated with motivation and emotion compared to exaggerated reactors. There were no reactivity group differences in subjective measures of the stressfulness and difficulty of and engagement with the stress task. Overall, the research reported in this thesis provides further evidence that blunted cardiovascular and cortisol reactions to stress are associated with a number of adverse health and behavioural outcomes and may be a peripheral marker of some form of disengagement in those areas of the brain that support motivated behaviour.

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Publications and conference presentations produced during the PhD

This thesis comprises of the following six original empirical papers:

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2. **Ginty, A.T.**, Phillips, A.C., Higgs, S., Heaney, J.L.J., & Carroll, D. (2012). Disordered eating behaviour is associated with blunted cortisol and cardiovascular reactions to acute psychological stress. *Psychoneuroendocrinology*, 37, 715-724.
3. **Ginty, A.T.**, Phillips, A.C., Der, G., Deary, I.J., and Carroll, D. (2011). Cognitive ability and simple reaction time predict cardiac reactivity in the West of Scotland Twenty-07 Study. *Psychophysiology*, 48, 1022-1027.
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5. **Ginty, A.T.**, Phillips, A.C., Der, G., Deary, I.J., Carroll, D. (2011). Heart rate reactivity is associated with future cognitive ability and cognitive change in a large community sample. *International Journal of Psychophysiology*, 82, 167-174.
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Journal Articles

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2. Carroll, D., **Ginty, A.T.**, Painter, R.C., Roseboom, T.J., Phillips, A.C., & de Rooij, S.R. (in press). Systolic blood pressure reactions to acute stress are associated with future hypertension status in the Dutch Famine Birth Cohort Study. *International Journal of Psychophysiology*.
3. Carroll, D., Bibbey, A., Roseboom, T.J., Phillips, A.C., **Ginty, A.T.**, & deRooij, S.R. (2012). Forced expiratory volume predicts cardiovascular and cortisol reactions to acute psychological stress even years later. *Psychophysiology*, 49, 866-872.

4. **Ginty, A.T.** & Conklin, S.M. (2012). Preliminary evidence that acute long-chain omega-3 supplementation reduces cardiovascular reactivity to mental stress: A randomized and placebo controlled trial, *Biological Psychology*, 89, 269-272.
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3. **Ginty, A.T.** (2012). Blood pressure, Measurement of. In M. Gellman and J.R. Turner (Eds.) *Encyclopedia of Behavioral Medicine*. New York, NY: Springer.
4. **Ginty, A.T.** (2012). Classical conditioning. In M. Gellman and J.R. Turner (Eds.) *Encyclopedia of Behavioral Medicine*. New York, NY: Springer.
5. **Ginty, A.T.** (2012). Diastolic blood pressure. In M. Gellman and J.R. Turner (Eds.) *Encyclopedia of Behavioral Medicine*. New York, NY: Springer.
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7. **Ginty, A.T.** (2012). Construct validity. In M. Gellman and J.R. Turner (Eds.) *Encyclopedia of Behavioral Medicine*. New York, NY: Springer.
8. **Ginty, A.T.** (2012). Heart rate. In M. Gellman and J.R. Turner (Eds.) *Encyclopedia of Behavioral Medicine*. New York, NY: Springer.
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List of Abbreviations

AH-4	Alice Heim-4
aMCC	anterior mid cingulate cortex
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CO	cardiac output
CRP	C-reactive protein
CRT	choice reaction time
DBP	diastolic blood pressure
DE	disordered eating
EABQ	Exercise Attitudes and Beliefs Questionnaire
EBQ	Exercise Beliefs Questionnaire
EDE-Q	Eating Disorders Examination-Questionnaire
EDQ	Exercise Dependence Questionnaire
EPQR-A	Eysneck Personality Questionnaire Revised- Abbreviated
ESR	erythrocyte sedimentation rate
fMRI	functional magnetic resonance imaging
HADS	Hospital Anxiety and Depression Scale
HPA	hypothalamic-pituitary adrenal
HR	heart rate
IMT	intima-media thickness
IQR	inter quartile range
ISEI-92	International Socio-Economic Index-92
LVMI	left ventricular mass index
MAP	mean arterial pressure
MDD	major depressive disorder
MSIT	Multi Source Interference Task
MT	memory test
PASAT	Paced Auditory Serial Additional Task
RDS	Reward Deficiency Syndrome
SBP	systolic blood pressure
SES	socio economic status
SV	stroke volume
TPR	total peripheral resistance

Chapter 1

General Introduction

The reactivity hypothesis postulates that individuals who show large magnitude cardiovascular reactions to acute psychological stress are at increased risk of developing cardiovascular disease (Obrist, 1981). This hypothesis has fuelled over 30 years of research and has resulted in a long-standing consensus among scientists that high reactivity has negative implications for future cardiovascular health (Lovallo & Gerin, 2003; Schwartz et al., 2003; Chida & Steptoe, 2010). Supportive evidence is provided by a number of large scale cross-sectional and prospective observational studies that show a positive association between the magnitude of cardiovascular reactions to acute psychological stress tasks and future blood pressure status and hypertension (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll et al., 2001; Everson, Kaplan, Goldberg, & Salonen, 1996; Newman, McGarvey, & Stelle, 1999; Matthews, Woodall, & Allen, 1993; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Treiber, Turner, Davis, & Strong, 1997); markers of systemic atherosclerosis, carotid intima wall thickness, or carotid atherosclerosis (Barnett, Spence, Manuck, & Jennings, 1997; Matthews et al., 1998; Everson et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998); and left ventricular mass and/or hypertrophy of the heart (Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Kapuku, et al., 1999; Murdison et al., 1998). Both qualitative reviews and meta-analyses of this evidence confirm the contention that exaggerated stress reactions signal poor future cardiovascular health (Gerin et al., 2000; Chida & Steptoe, 2010; Schwartz et al., 2003; Taylor, Kamarck, & Dianzumba, 2003; Treiber et al., 2003). The empirical studies cited above are summarised in Table 1.1 at the end of this chapter.

The metabolic system and increased cardiovascular reactions to stress

When an individual exercises, both the cardiovascular and metabolic system respond in a synchronised fashion, with increases in cardiovascular activity matching the increased

requirement for energy to meet the needs of the exercising skeletal muscles. In this context, then, increased cardiovascular activity is justified and regarded as beneficial (Carroll, Phillips, & Balanos, 2009b; Navare & Thompson, 2003). In contrast, when an individual reacts to acute psychological stress the increases in cardiovascular activity are in excess of what is needed to meet more modest increases in energy expenditure (Carroll et al., 2009b; Turner & Carroll, 1985; Obrist, 1981). The heart is working harder than the rest of the body, and the body is not maintaining homeostasis. This has been shown in numerous laboratory studies using stress tasks such as video games, mental arithmetic, and aversive reaction time avoidance tasks (Carroll, Turner, & Hellawell, 1986; Carroll, Turner, & Prasad, 1986; Langer et al., 1985; Turner & Carroll, 1985; Carroll, Harris, & Cross, 1991; Sherwood, Allen, Obrist, & Langer, 1986). Additionally, there is supportive evidence from field studies of novice parachutists immediately prior to jumping (Stromme, Wikeby, Blix, & Ursin, 1978) and in helicopter and transport aircraft pilots during difficult flight maneuvers (Blix, Stromme, & Ursin, 1974). Such metabolically inappropriate responses of the cardiovascular system form the backbone of the reactivity hypothesis (Obrist, 1981). Failing to mount a cardiovascular reaction to such acute stress exposures or showing only a slight response would appear to be the more metabolically appropriate adjustment and could be regarded as the adaptive response pattern.

Blunted reactions to stress

Accordingly, low or blunted cardiovascular reactivity to acute stress has, by implication, been regarded as benign or even protective (Carroll, Lovallo, & Phillips, 2009a).

However, recent evidence suggests that blunted cardiovascular and, indeed, blunted cortisol reactivity to acute stress may be implicated in adverse health and behavioural outcomes (Carroll et al. 2009a, Lovallo, 2011). Recent epidemiological evidence shows that blunted cardiovascular and cortisol reactivity is associated with obesity, symptoms of

depression, and poor self-reported health, and indeed predicts the likelihood of becoming obese (Carroll, Phillips, & Der, 2008); depressed (Carroll, Phillips, Hunt, & Der, 2007; Phillips, Hunt, Der, & Carroll, 2011; de Rooij, Schene, Phillips, & Roseboom, 2010); and subjectively in poor health (de Rooij & Roseboom, 2010; Phillips, Der, & Carroll, 2009). This evidence has emerged mainly from two large epidemiological datasets, the West-of-Scotland Twenty-07 Study and the Dutch Famine Birth Cohort Study; two independent prospective epidemiological studies deploying different psychological stress tasks in distinct populations. However, there is evidence from elsewhere confirming the link between low reactivity and depression (York et al. 2007; Salomon, Clift, Karlsdottir, & Rottenberg, 2009; Schwerdtfeger & Rosenkaimer, 2011). The relevant empirical studies relating blunted stress reactivity to adverse health and behavioural outcomes are summarised in Table 1.2. at the end of this chapter.

Addictions and blunted responses to stress

In addition to obesity, depression, and poor self-reported health, low cardiovascular and cortisol reactions to acute psychological stress are also characteristic of individuals with addictive behaviours. For example, blunted reactivity characterises both smokers (al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Kirschbaum, Strasburger, & Langkrar, 1993; Phillips, Der, Hunt, & Carroll, 2009) and those with alcohol and other substance addictions (Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002). Habitual smokers show a diminished salivary and plasma cortisol stress response (Al' Absi et al., 2003; Kirschbaum, Strasburger, & Langkrar, 1993; Rohleder & Kirschbaum, 2006) as well as blunted cardiovascular (Girdler, Jamner, Jarvik, Soles, & Shapiro, 1997; Phillips, Der, Hunt, & Carroll, 2009; Roy, Steptoe, & Kirschbaum, 1994) reactions to multiple psychological stress tasks compared to non-smokers. Blunted stress reactivity in smokers cannot be attributed to

temporary abstinence during a stress testing session, as smokers wearing nicotine patches still show diminished reactivity (Girdler et al., 1997). Blunted stress reactions also predict relapse in smokers who have quit (al' Absi, Hatsukami, & Davis, 2005; al' Absi et al., 2006), suggesting that blunted stress reactivity may have substantial prognostic value. Individuals addicted to alcohol have also been found to exhibit blunted cardiovascular and/or cortisol stress reactivity (Lovallo et al., 2000; Panknin et al., 2002), as have the adolescent offspring of alcoholic parents (Sorocco, Lovallo, Vincent, & Collins, 2006; Moss, Vanyukov, Yao, & Kirillova, 1999), implying that blunted reactivity may pre-date addictive behaviour. In light of the accumulating evidence supporting an association between blunted stress reactivity and addiction, and the emerging evidence relating blunted reactivity to other unhealthy behaviours and outcomes, it would now appear that both extremes, exaggerated and diminished reactivity, may reflect a dysregulation in the body's response to stress (Lovallo, 2011). The relevant empirical studies relating blunted stress reactivity to addictive behaviours are summarised in Table 1.3. at the end of this chapter.

Motivational dysregulation and stress responses

Based on research showing the relationship between low reactivity and adverse outcomes such as obesity, depression, and addiction, it has been proposed that blunted physiological stress reactivity may be a peripheral marker of central motivational dysregulation (Carroll et al., 2009a; Carroll, Phillips, & Lovallo, 2011). The term 'central motivational dysregulation' refers to a dysregulation in the physiological systems in the brain that support motivated behaviour, i.e., the suboptimal functioning of those systems converging at the striatum and ventromedial prefrontal cortex that appear to shape the motivation of behaviour (Carroll et al., 2011). Clinically based research shows diminished responses to reward in individuals with depression, obesity, and addiction in areas of the brain

associated with motivation and reward (Bylsma, Morris, & Rottenberg, 2008; McFarland & Klein, 2009; Epstein, et al., 2006; Stice, Spoor, Bohon, & Small, 2008; Wrase et al., 2007; Kalivas & Volkow, 2005; Reuter et al., 2005). Individuals with addictions, depression, and obesity feel a lack of satisfaction and gratification because of a failure in certain brain systems (e.g. limbic lobe) which then results in an increased uptake in the unhealthy behaviours to try to achieve these feelings (Blum et al., 2011). It appears that these disorders are also characterized by blunted reactions to acute psychological stress and, accordingly, it seems reasonable to hypothesise that blunted responses to stress may be a peripheral marker of dysregulation of these central neural motivational systems (Carroll et al., 2009a).

Responses to stress and non-substance abuse addictions

Substantial research attention has been directed at cardiovascular and cortisol reactivity and substance addictions (al' Absi et al., 2003; Kirschbaum, Strasburger, & Langkrar, 1993; Lovallo et al., 2000; Panknin et al., 2002; al' Absi et al., 2005; al' Absi et al., 2006; Soroccco et al., 2006; Moss et al., 1999). However, if low cardiovascular and cortisol reactivity is a marker of addictive behaviour in general and linked to risk of addiction (Lovallo, 2006; Lovallo; 2011), then it should be evident in other addictive behaviours. The first aim of this thesis is to examine the relationship between low reactivity in non-substance abuse addictive behaviours.

Although properly regarded as healthy and beneficial, exercise can become excessive and has the potential to become a damaging obsession (Morgan, 1979). Individuals who exhibit what has come to be called 'exercise dependence' display similar behavioural patterns as those with substance addictions: increasing tolerance to exercise; experience of withdrawal symptoms on cessation of exercise; continued exercise despite medical

contraindications; disturbances in psychological functioning; and exercise interference with their relationships or work (Bamber, Cockerill, & Carroll, 2000, Bamber, Cockerill, Rodgers, & Carroll, 2003, Robbins & Joseph, 1985, Yates, Leehey, & Shisslak, 1983). It would appear that for exercise dependent individuals exercise becomes all consuming and they increasingly need to exercise to derive any sort of reward (Morgan, 1979). In short, exercise dependence would seem to be indicative of motivational dysregulation. If blunted physiological stress reactions are a marker for a dysregulation in the motivational systems of the brain associated with reward, then individuals with exercise dependence should display blunted responses to stress compared with their non-dependent exercising counterparts.

Stress reactivity and disordered eating

Individuals exhibiting disordered eating behaviour, particularly bulimia, also appear to be characterised by behavioural and motivational dysregulation similar to that of those suffering from addictions. The obsession with controlling food is overpowering and this has consequences for overall functioning (Cattanach et al., 1988). Similar to addiction, stressful events can have detrimental effects on behaviours; increased perceptions of stress and negative affect can precede binges and ultimately contribute to the aetiology and maintenance of bulimia nervosa (Abram & Joseph, 1987; Cattanach, Malley, & Rodin, 1988; Cattanach & Rodin, 1988; Lingswiler, Crowther, & Stephens, 1989; Tropp, Holbrey, Trowler, & Treasure, 1994). Although the role of stress in disordered eating is well documented (Crowther & Chernyk, 1986; Lacey, Coker, & Birtchnell, 1986; Cattanach & Rodin, 1988; Koo-Loeb, Costello, Light, & Girdler, 2000), previous research offers no clear consensus about the relative magnitude of physiological reactions to stress of individuals who show disordered eating behaviour (Pirke et al., 1992; Messerli-Burgy et al., 2010; Koo-Loeb, Pedersen, & Girdler, 1998; Cattanach et al., 1988; Koo-Loeb et al.,

2000). Recent imaging research has shown that women with bulimia have hypo-functioning of the brain reward system (Frank et al., 2006) and have similar reward responses to food as individuals with obesity (Bohon & Stice, 2011). In sum, it would appear that women with bulimia have problems with central motivational functioning similar to those with addiction, depression, and obesity and thus would be expected to display blunted physiological reactions to stress.

Stress reactivity and cognitive ability

Optimal cognitive performance requires the integrity of motivational systems (Busato, Prins, Elshout, & Hamaker, 2000; Dweck, 1986; McClelland, Atkinson, Clark, & Lowell, 1953; Pintrich & Schunk, 1986). If low cardiovascular stress reactivity is a marker of dysregulation of the central neural circuits that support motivation (Carroll et al., 2009a; Carroll et al., 2011), then it would be expected, from this perspective, that lower rather than higher cardiovascular reactivity would be associated with poorer subsequent cognitive function.

There is now substantial evidence that hypertension is associated prospectively with poorer cognitive function (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Launer, Masaki, Petrovich, Foley, & Havlic, 1995; Singh-Manoux & Marmot, 2005; Waldstein, 2003), as well as evidence implicating systemic inflammation more generally in subsequent cognitive impairment. For example, C-reactive protein (CRP), an acute-phase protein synthesised in the liver and widely used as a marker of inflammation, is associated with cognitive function. A review showed a relationship between high concentrations of CRP and cognitive decline (Kuo et al., 2005). Since then, two large scale studies have shown both prospective (Laurin et al., 2009) and cross-sectional (Schram et al., 2007) associations between poorer cognitive function and higher CRP. Cognitive ability has also

been associated with erythrocyte sedimentation rate (ESR). ESR is also a marker of inflammation; it is the aggregation of erythrocytes and their rate of sedimentation in a test tube, which is determined by the increase in proteins, such as globulins and fibrinogen (van Leeuwen & van Rijswijk, 1994; Phillips et al., 2011). In a recent very large-scale study there was a negative cross-sectional association between cognitive ability and ESR, those with higher ESR values showed lower cognitive abilities (Karlsson, Ahlborg, Dalman, & Hemmingsson, 2010). However, cognitive ability earlier in life has also been found to predict systemic inflammation in middle age, suggesting the possibility of a bidirectional relationship (Phillips et al., 2011). If excessive reactivity contributes to inflammatory cardiovascular disease and inflammation is associated with impaired cognitive function, we might expect cardiovascular stress reactivity to be negatively associated with cognitive ability, i.e. those with high cardiovascular reactivity would be characterized by poor cognitive function.

Little is known about the association between cardiovascular stress reactivity and cognitive function. Research to date has been inconclusive, with two studies reporting a positive relationship (DeGangi et al., 1991; Duschek et al., 2009) and two reporting no relationship (Bucks & Selios, 1994; Wright et al., 2005). There is also no clear consensus about the relationship between cortisol reactivity and cognitive ability. High cortisol reactivity was reported to be associated with poorer cognitive performance (Wright et al., 2005), high cortisol reactivity has also been associated with both better (Domes, Heinrichs, Reichwald, & Hautzinger, 2002) and poorer memory performance (Lupien et al., 1997). Finally, high magnitude cortisol reactivity has been observed to be related to better cognitive executive function (Blair, Granger, & Razza, 2005) and better dichotic listening performance (al' Absi, Hugdahl, & Lovallo, 2002).

Further, with one exception (Wright et al., 2005), all of the previous studies were small scale ($N \leq 60$) and did not adjust for potential confounding variables. Most importantly, all of these previous studies measured cognitive ability as performance on the stress reactivity challenge. Examining the association between cognitive ability and cardiovascular reactivity in large populations using cognitive tests that are independent of the stress task, thus not confounded with it, are required to properly examine the association between cognitive ability and stress reactivity. Given the possibility that cognitive ability and inflammation are related in a bidirectional fashion, both retrospective and prospective assessment, in addition to cross-sectional analyses, could prove instructive, if poor cognitive ability is associated with blunted reactivity, this could be regarded as providing further evidence that blunted reactivity is a marker of central motivational dysregulation.

Neural correlates of reactivity

As previously described, many of the behavioural and health corollaries associated with low stress reactivity would seem to be characterised by hypo-activation in the motivational areas of the brain. Evidence shows decreased brain activation during fMRI tasks in participants at risk of (Mannie, Taylor, Harmer, Cowen, & Norbury, 2011) and with depression (Holson et al., 2011), at risk for (Glahn, Lovallo, & Fox, 2007) and with alcoholism (Beck et al., 2009), and with bulimia (Marsh et al., 2011; Joos et al., 2011). Hypoactivation was also observed in those with obesity (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008), weight gain (Stice, Yokum, Blum, & Bohon, 2010) and higher body mass index (Batterink, Yokum, & Stice, 2010). These studies observed responses to stimuli aimed at provoking activation in frontolimbic regions of the brain (e.g. go/no go tasks and provocative images). Studies examining activation during an acute psychological stress task in those with behaviours and health corollaries associated with blunted stress reactivity are almost non-existent.

Nevertheless, there is preliminary evidence that individuals who show blunted cardiovascular stress reactions also show hypoactivation in limbic regions during stress exposure. Individual differences in cardiovascular reactivity to stress has been reported to relate to differences in activation in the perigenual and mid-anterior regions of cingulate cortex (Gianaros et al., 2005a), the posterior cingulate cortex (Gianaros, May, Siegle, & Jennings, 2005b), and the amygdala (Gianaros et al, 2008). For example, in a study that examined the neural responses, using fMRI, to a standard stress task of eight high and eight low cardiovascular reactors, the low reactors showed less activation in the posterior cingulate cortex when exposed to stress (Gianaros et al., 2005b). At the time this study was conducted, nothing was known about the behavioural correlates of blunted stress reactivity and so the study's theoretical interest was very much directed at the neural correlates of exaggerated peripheral stress responses.

To truly understand the underlying neural mechanisms of individuals with extreme responses to stress, both exaggerated and diminished, an fMRI study is needed to examine activating during stress in confirmed extreme cardiovascular responders. Participants need to be selected on the basis of their cardiovascular responses and not for their health behaviours. Testing neural activation differences during a standardised acute psychological stress task will provide evidence to either support or challenge the overarching hypothesis that blunted reactivity is a marker for dysregulation in the motivational systems of the brain associated with reward.

Present thesis

The present thesis comprises of three experimental studies and three secondary analyses of epidemiological data that have yielded six papers examining the associations between behaviour, cognitive ability, and neural activation in individuals who exhibit blunted

cardiovascular and/or cortisol reactions to acute psychological stress. The first paper aimed to confirm that blunted cardiovascular and cortisol reactivity is also a marker of non-substance dependencies by examining the relationship between reactivity and exercise dependence. It was hypothesised that those who were exercise dependent would show blunted stress reactivity compared to controls. The second paper aimed to determine whether blunted reactivity was also characteristic of other unhealthy behaviours, in this case, disordered eating. It was hypothesised that those with disordered eating would show blunted reactions to mental stress relative to controls in both branches of the stress effector system: hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system. The third, fourth, and fifth chapters of this thesis comprise of three original papers looking at the associations between cognitive ability and cardiovascular reactivity, retrospectively, cross-sectionally, and prospectively. It was hypothesised that lower cardiovascular reactivity would be associated with poorer cognitive ability. For the prospective analyses, it was also hypothesised that lower cardiovascular reactivity would predict faster cognitive decline between five and 12 years following stress testing. Finally, the last empirical chapter in this thesis examines, using fMRI, neural activation differences between confirmed high and low cardiac responders when exposed to a standardised stress task in the fMRI scanner. It was hypothesised that blunted cardiac reactors would exhibit lower activation differences between stress and control exposures in those areas of the brain implicated in motivation compared to high reactors.

My contribution to the studies reported in the thesis

Study 1 was devised jointly by all four authors. However, I ran the study and collected most of the data. JH performed the cortisol assays. I undertook the statistical analyses with input from DC. With JH and DC, I drafted the manuscript, with all four authors contributing to the final version of the paper. The idea for study 2 was mine, and all

authors helped plan the design. Again I carried out the study, and analysed all the data, including, in this case, carrying out the cortisol assays and Doppler echocardiography scans. Statistical analyses were undertaken by me under the supervision of DC. With input from DC I drafted the manuscript and all five authors contributed to the final version of the paper. The idea to look at cognitive ability and reactivity was mine. DC and AP helped me secure the data from Glasgow and Amsterdam. I undertook the statistical analyses with occasional input from DC, AP, and GD (Glasgow) and S deR (Amsterdam). I drafted the papers with input from DC and AP. All authors contributed to the final version of the manuscripts. The final study was again my idea, and I designed it with input from all the authors. With the exception of two participants, the extreme low and high cardiac reactors were selected by me from laboratory stress testing that I conducted over a period of two years. I conducted all testing, analysis of the Doppler echocardiography for that study, and statistical tests to select participants. There was no overlap with participants who took part in the exercise dependence and bulimia studies. I conducted the fMRI part of the study, and, with input from SD and PG, analysed and interpreted the data. Again I drafted the paper with primary input from DC; as before all five authors contributed to the final version of the manuscript.

Table 1.1. Summary of empirical studies examining the relationship between cardiovascular reactions to acute psychological stress and negative cardiovascular outcomes.

Author	Participants	Stress task used	Outcome measure	Covariates	Results	Effect size
Blood pressure/Hypertension						
Carroll, Ring, Hunt, Ford, & Macintyre, 2003	N = 990 Mean age (SD) years = 41.7 (14.81) 55% female	Paced auditory serial addition task (PASAT)	Future blood pressure (BP) status (~5 years later)	Age, body mass index, baseline systolic blood pressure (SBP) at stress testing	SBP reactivity predicted blood pressure 5 years later. Blood pressure reactivity was associated with the extent of upward drift in resting blood pressure over time.	SBP reactivity accounted for 2.3% of variance in follow-up SBP. SBP reactivity predicted upward drift in BP more than follow-up SBP; SBP reactivity accounted for 3.6% of variance in upward drift in SBP.
Carroll, Smith, Sheffield, Shipley, & Marmot, 1995	N = 1003, civil servants Mean age (SD) years = 44.1 (5.92) 100% male	Raven's matrices	Future BP (~5 years later)	Age, laboratory baseline cardiovascular values, initial screening cardiovascular values	SBP reactivity accounted for some of the variance in changes of BP over 5 years, but was not as strong a predictor as resting BP or casual (initial screening) BP.	SBP reactivity accounted for 1% of future SBP.
Carroll, Smith, Shipley, Steptoe, Brunner, & Marmot, 2001	N = 796, civil servants Mean age (SD) years = 44.1 (5.92) 100% male	Raven's matrices	Future BP (~10 years later)	Age, laboratory baseline cardiovascular values, initial screening cardiovascular values	SBP reactivity accounted for part of the variance in changes of BP over 10 years, but was not as strong a predictor as resting BP or casual (initial screening) BP.	SBP reactivity accounted for 1% of future SBP.

					Diastolic blood pressure (DBP) reactivity significantly predicted DBP 10 years later, but did not survive adjustment for confounding variables.	
Everson, Kaplan, Goldberg, & Salonen, 1996	N = 508 Mean age (SD) years = 51.0 (6.7), never had diagnosis of hypertension and not on anti-hypertensive medication 100% male	Anticipation of an exercise task where they knew their results would be an indicator of their cardiovascular health status, also told to perform at their best level	Hypertensive status (~4 years later)	Age, smoking, alcohol consumption, physical activity, body mass index, positive maternal and paternal histories of hypertension, baseline resting cardiovascular values	Large BP responses in anticipation of the exercise task were related to increasingly greater risk of hypertensive pressures 4 years later. There was a dose response between SBP reactivity and hypertension 4 years later.	Those in highest quartile for SBP reactivity have an Odds Ratio (OR) = 4.13, and those in the highest quartile for DBP reactivity have an OR = 3.43 in terms of increased risk for hypertension status 4 years later.
Newman, McGarvey, & Steele, 1999	N = 83, (N = 34) American Samoans and (N = 49) Western Samoans Mean age (SD) years = Male American Samoan: 13.2 (0.8) Female American Samoan: 12.9 (0.6) Male Western Samoan: 12.3 (0.8) Female Western Samoan: 12.4 (0.9) 49% female	Video game	Future BP (~3.5 years later)	Baseline BP level, age, and BMI	Greater SBP reactivity was related to higher resting SBP 3.5 years later	SBP reactivity accounted for an additional 4% of the variance in resting SBP 3.5 years later.

Matthews, Woodall, & Allen, 1993	N = 370, middle-aged adults (N = 206) and their children (N = 164) Mean age (SD) years = Men: 44.1 (6.5) Women: 41.8 (5.3) Boys: 13.2 (2.8) Girls: 13.6 (2.4) 55% female	Serial subtraction, mirror tracing, and isometric handgrip	Follow-up resting BP (~6.5 years later)	Age, BMI, resting BP, and length of follow-up	Elevated SBP and DBP reactions to stress were associated with higher resting DBP 6.5 years later among adults. Higher SBP and DBP reactions to stress were associated with higher resting SBP and DBP 6.5 years later among male children.	r^2 values ranged from .13 - .37 in significant analyses.
Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998	N = 3364 Mean age = 27.0 years 53% female	Video game, mirror tracing, and cold pressor task	Resting BP and hypertensive status (~5 years later)	Age, BMI, alcohol intake, clinical baseline BP, family history of high BP, cigarette smoking status, examination site, education level at 2 nd follow-up, changes in BMI and alcohol intake over 5-year period	The video game stress task predicted BP increases over a 5-year period in men.	Men with SBP reactivity values of: 5 mmHg had an OR = 0.8, 10 mmHg had an OR = 1.0, 20 mmHg had an OR = 1.4, 30 mmHg had an OR = 2.0, of having a significant blood pressure increase 5-years later.
Treiber, Turner, Davids, & Strong, 1997	N = 246, children with a familial history of essential hypertension Mean age (SD) years = White Males: 10.3 (2.3) White Females: 10.6 (2.5) Black Males: 11.2 (2.6)	Video game, postural change, forehead cold pressor	Resting BP (~5 years later)	Age, height, weight, adiposity, body surface area, social economic status (SES)	SBP and DBP reactivity to the video game and postural change stress tasks significantly predicted future resting SBP and DBP. In most cases SBP and DBP reactivity was more strongly associated with resting	SBP reactivity response to video game, $r^2 = .2$; SBP mean response to video game $r^2 = .52$; postural challenge mean response, $r^2 = .52$. DBP mean response to video game, $r^2 = .38$; postural

	Black Females: 10.8 (2.4) 51% female				SBP than other risk factors such as: height, weight, adiposity, age, and SES.	challenge mean response, $r^2 = .35$.
Carotid atherosclerosis						
Barnett, Spence, Manuck, & Jennings, 1997	N = 351, hospital outpatients and volunteers Mean age (SD) years = Men: 48.0 (11.0) Women: 53.0 (10.0) 45% female	Stroop Color-Word Interference Task	Severity and progression of carotid atherosclerosis	For 2-year change: plaque area at time 1, age, change in SBP, pre-ejection period, Chol:HDL, body mass index	Correlated at baseline and significant predictor of the progression of extent of atherosclerosis.	SBP reactivity accounted for 7% of variance in a model predicting development of plaque during 2 years.
Matthews, Owens, Kuller, Sutton-Tyrrell, Lassila, & Wolfson, 1998	N = 254 Men age (SD) years = 55.7 (1.8) 100% female	Mirror tracing task, Speech task	Carotid atherosclerosis (intima-media thickness (IMT) and focal plaque in the common carotid artery, bulb, internal carotid artery) Measured ~2.3 years later	Age, use of hormone replacement therapy, baseline BP or HR at stress testing, ever-smoking status, triglycerides and BP	IMT was related to magnitude of change in pulse pressure across all three tasks and plaque index (only mirror tracing task).	IMT and pulse pressure reactivity, $r = 0.17$. Plaque index associated with pulse pressure reactivity for women with plaque score ≥ 2 , OR = 1.47, fully adjusted.
Everson, Lynch, Chesney, Kaplan, Goldberg, Shade, Cohen, Salonen, & Salonen, 1997	N = 591 M age (SD) years = Low job demands, low reactors = 47.6 (5.4) Low job demands, high reactors = 50.7 (5.9) High job demands, high reactors = 47.8 (5.4)	Anticipation of exercise (encouraged to perform at their best level and knew that results of the test would be in indicator of their cardiovascular health status)	Change in IMT of the right and left common carotid arteries from baseline to ~4-year follow up	Age, baseline IMT, zooming depth of the ultrasound scan, sonographer, participation in the placebo or treatment arm of an unrelated clinical trial of parvastatin, resting SBP, apolipoprotein B concentration, high density lipoprotein cholesterol-2 concentration, body mass	Men who have higher reactivity and have a highly demanding work environment have a greater progression of carotid atherosclerosis than men with low reactivity or had fewer demands or both have: increases in IMT and	High reactivity and highly demanding work predicted 10-40% progression of mean and maximum IMT and plaque height. Men with high reactivity and a highly demanding work life with 20%

	High job demands, high reactors = 51.6 (5.6) 100% male			index, cigarette smoking, alcohol consumption, use of antihypertensive or antihyperlipidaemic drugs, and history of diabetes	plaque height.	stenosis or non-stenotic plaque at baseline had more than a 46% greater atherosclerotic progression than rest of population.
Lynch, Everson, Kaplan, Salonen, & Salonen, 1998	N = 882 Ages of participants = 42, 48, 54, and 60 100% male	Anticipation of exercise (encouraged to perform at their best level and knew that results of the test would be in indicator of their cardiovascular health status)	4 year progression of IMT, plaque height, and mean thickness	Age, baseline thickness, high-density lipoprotein 2, apolipoprotein B, triglycerides, SBP, body mass index, smoking, alcohol, and treatment for hypertension or hyperlipidemia	Men who had heightened cardiovascular responsiveness to stress and those who had been born into poor families, received little education or had low incomes had greatest 4-year progression of carotid atherosclerosis.	F values for SES and reactivity interaction with: IMT (3.19) and plaque height (5.16). F value for education and reactivity interaction with: IMT (4.18) and plaque height (2.76).
Left ventricular mass						
Georgiades, Lemne, De Faire, Lindvall, & Fredrikson, 1997	N = 66 Mean age (SD) years = 47.0 (5.0) 100% male	Mental arithmetic (serial subtraction), isometric muscle contraction	Left ventricular mass index (LVMI) over a 3-year period	Baseline left ventricular mass and casual clinical, resting, ambulatory 24-h of SBP, DBP, and MAP measurements	BP reactivity measurements predict the development of LVMI better than casual or resting BP measurements	MAP reactivity explained 15% of LVMI over and above initial LVMI values and explained 39% of the variance between time points.
Kapuku, Treiber, Davis, Harshfield, Cook, & Mensah, 1999	N = 146 Mean age (SD) years = 14.2 (1.8) 61% female	Orthostasis, car-driving stimulation, video game, and forehead cold press	Left ventricular mass (~2.3 years apart)	Baseline echocardiograph parameters, sex, race, weight, BMI, resting haemodynamics, ambulatory BP measures	SBP and total peripheral resistance reactivity were positively related to left ventricular mass 2.3 years later.	SBP responses to all tasks, $r = 0.22 - 0.33$. TPR responses to all tasks, $r = 0.19 - 0.23$.

Table 1.2. Summary of empirical studies relating blunted stress reactivity to adverse health and behavioural outcomes.

Author	Participants	Stress task used	Outcome measure	Covariates	Results	Effect size
Obesity						
Carroll, Phillips, & Der, 2008	N = 1647 M age (SD) years = 41.8 (14.44) 54% female	Paced auditory serial addition task (PASAT)	Adiposity and obesity cross-sectionally and ~5 years later	Age, sex, SES, task performance, medication, smoking status, baseline cardiovascular values	Obese participants exhibited smaller HR reactions to stress. Greater BMI and waist-hip ratio were associated with lower HR reactivity. Low HR reactivity predicted which participants were more likely to become obese in 5 years.	Obese vs. non-obese and HR reactions to stress, $\eta^2 = 0.010$. Associations between BMI and HR reactivity, $r^2 = 0.020$. Low HR reactivity predicted obesity 5 years later, OR = 0.97 (fully adjusted).
Depression/depressive symptoms						
Carroll, Phillips, Hunt, & Der, 2007	N = 1608 M age (SD) years = 42.3 (15.48) 54% female	PASAT	Depressive symptoms (HADS)	Age, sex, SES, BMI, task performance, medication status (taking or not taking antidepressives, anxiolytics, or anti-hypertensives), and baseline cardiovascular values	Depression scores negatively associated with SBP and HR reactions to acute psychological stress (fully adjusted).	SBP reactivity, $\Delta r^2 = 0.003$. HR reactivity, $\Delta r^2 = 0.002$. Binary, cut-off HADS score ≥ 8 : SBP reactivity, $\Delta r^2 = 0.002$. HR reactivity, $\Delta r^2 = 0.005$.
Phillips, Hunt, Der, & Carroll, 2011	N = 1608 M age (SD) years = 42.3 (15.48) 54% female	PASAT	Depressive symptoms ~5 years later	HADS depression scores at time of stress testing, age, sex, SES, task performance, antidepressive medication status, anti-hypertension medication status	Low HR reactivity predicted future depression scores, fully adjusted, including earlier depression symptomatology.	Low HR reactivity predicted depression ~5 years later, $\Delta r^2 = 0.002$.
de Rooij, Schene,	N = 725	Stroop test, mirror-	Depression and anxiety cross-	Smoking status, sex, use of anti-hypertensive	Depressive and anxiety symptoms were related to	1% of variance of reactivity (BP, HR, and cortisol)

Phillips, & Roseboom, 2010	Mean age (SD) years = 58.3 (0.9) 53% female	tracing task, and speech task	sectionally	medication, alcohol consumption, SES, BMI	decreased cortisol and cardiovascular responses to acute psychological stress.	explained by HADS scores or a diagnosis of depression or anxiety.
Salomon, Clift, Karlsdottir, & Rottenberg, 2009	N = 50, Major Depressive Disorder (MDD) (N = 25), Healthy controls (N = 25) Mean age (SD) years = MDD = 30.4 (9.4) Controls = 32.0 (11.9) 68% female	Public speaking task and mirror tracing task	Depressive symptomatology, examining differences between MDD and controls	Gender	Participants with MDD exhibited significantly lower SBP, HR, and cardiac output reactivity during a speech task and lower HR reactivity during a mirror tracing task compared with controls	Reactivity effects: Speech preparation SBP: $\eta^2 = .085$ HR: $\eta^2 = .092$ CO: $\eta^2 = .189$ Speech delivery HR: $\eta^2 = .208$ CO: $\eta^2 = .093$ Mirror tracing HR: $\eta^2 = .118$
York, Hassan, Li, Li, Fillingim, & Sheps, 2007	N = 128, patients with coronary artery disease (CAD) Mean age (SD) years = 63.0 (8.0) 43% female	Public speaking task	Depression symptomatology (Beck Depression Inventory)	Baseline cardiovascular values, age, diabetes status, and antidepressant, β block and calcium-channel antagonist use	Increased depressive symptomatology was related to lower cardiovascular reactivity.	Depression scores accounted for an additional 5% change in HR in fully adjusted models.
Self-reported health						
de Rooij & Roseboom, 2010	N = 725 Mean age (SD) years = 58.3 (0.9) 53% female	Stroop test, mirror-tracing task, and speech task	Self-reported health	Age, sex, SES, BMI, use of hypertensive medication, baseline cardiovascular and cortisol measures where appropriate	Poorer self reported health was associated with lower cardiovascular and cortisol reactivity.	Reactivity predicting poorer self reported health: Cortisol: $\beta = .30$ SBP: OR = 2.7 DBP: OR = 1.2 HR: OR = 1.2

Phillips, Der, & Carroll, 2009	N = 1647 Mean age (SD) years = 41.8 (15.4) 54% female	PASAT	Self-reported health cross- sectionally and prospectively (~5 years later)	Baseline cardiovascular levels, age, sex, SES, stress task performance scores, BMI, and anti- hypertensive medication status	Fair or poor self-reported health was related to blunted cardiovascular reactions to stress.	Cross-sectionally: SBP: $\eta^2 = .003$ DBP: $\eta^2 = .004$ Prospectively: DBP: OR = 1.02 HR: OR = 1.02
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Table 1.3. Summary of empirical studies relating blunted stress reactivity to addictive behaviours.

Author	Participants	Stress Task	Covariates	Results
Smoking				
al' Absi, Hatsukami, & Davis, 2005	N = 72 Mean age (SD) years = 36.0 (1.7) Successful quitters: N = 18 Relapsers: N = 54 46% female	Public speaking, Serial addition task, PASAT	Did not differ in: BMI, education, average number hours of sleep, physical activity, age of first cigarette, daily smoking rate, duration of smoking at current rate, carbon monoxide levels during screenings, ratings of motivation to quit, number of previous attempts	Smokers who relapsed exhibited lower DBP increases during stress than successful quitters. Regression analyses showed that lower plasma cortisol and BP reactions to stress were related to shorter time to relapse.
al' Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003	N = 70 Smokers who continued to smoke: N = 17; M age (SD) years = 22.3 (2.0); 59% female Smokers who were abstinent for 18 h prior: N = 21; M age (SD) years = 23.5 (1.7); 48% female Non-smokers: N = 32; M age (SD) years = 23.2 (1.3); 56% female	Speech task	No group differences in BMI, physical activity, education, depression, anxiety	Smokers showed attenuated cortisol and SBP responses to the stress task.
Girdler, Jamner, Jarvik, Soles, & Shapiro, 1997	N = 76, (smokers N = 41; non-smokers N = 35) Mean age = not reported, aged between 20 - 40 years 61% female	Speech task, Stroop Test, PASAT, Cold pressor	Not influenced by oral contraceptives or presence of nicotine (patch or placebo patch)	Female smokers had significantly blunted HR and CO reactions to stress and significantly greater TPR reactions to stress compared to non-smokers. No group differences for males.
Kirschbaum, Strasburger, & Langkrar, 1993	N = 20 (N = 10 smokers, N = 10 non-smokers) Mean age (SD) years = 24.7 (3.3) 0% female	Public speaking and mental arithmetic (serial subtraction)	Baseline cardiovascular values	Smokers showed attenuated cortisol responses to stress, no HR differences between groups

Phillips, Der, Hunt, & Carroll, 2009	N = 1647 (N = 593 smokers, N = 338 ex-smokers, N = 715 never smokers) Mean age (SD) years = 41.8 (15.4) 54% female	PASAT	Baseline values, age, sex, SES, BMI, antihypertensive medication status, performance score on PASAT	Smokers showed significantly smaller SBP and DBP reactions to stress than ex and non-smokers and smokers and ex-smokers had lower HR reactivity than never smokers
Roy, Steptoe, & Kirschbaum, 1994	N = 86, (smokers N = 34; non-smokers N = 52) Mean age (SD) years = 25.1 (3.6) 100% male	Mental arithmetic, speech task	Could not be accounted for group differences in: family history of cardiovascular disease, alcohol consumption, exercise levels, life events, daily stress and social support, anxiety, anger expression, and depression.	SBP, DBP, HR and cortisol responses were blunted in smokers compared to non-smokers in response to mental arithmetic task.
Alcoholism				
Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000	N = 30 Hospitalized alcohol dependent patients: N = 10; M age (SD) years = 40.0 (2.9) Hospitalized alcohol and stimulant dependent patients: N = 10; M age (SD) years = 38.0 (2.0) Healthy controls: N = 10; M age (SD) years = 40.0 (2.9) 100% male	Orthostatic challenge, public speaking	Tested to see if glucose regulation, clinical depression, PTSD, or demographic or anthropometric characteristics were different/influenced results	Control participants had large cortisol responses to stress tasks; alcohol dependent and alcohol/stimulant dependent patients exhibited no cortisol responses to stress.
Panknin, Dickensheets, Nixon, & Lovallo, 2002	N = 30 Alcohol dependent (abstinent for 21 to 28 days): N = 20; Mean age (SD) years = 38.0 (2.0) Healthy controls: N = 10; Mean age (SD) years = 40 (2.0) 100% male	Orthostatic challenge, public speaking	Baseline cardiovascular values, age, education, body-surface area, height, weight, ethnicity, nicotine use and chronicity, caffeine use	Alcohol dependent individuals had significantly lower HR responses to stress than healthy controls. MAP and SBP reactions were also lower than those of healthy controls, but differences were not statistically significant.
Sorocco, Lovallo, Vincent, & Collins, 2006	N = 186 healthy social drinkers with no personal history of drug dependence Family history of one or two alcoholic parents (FH+): N = 91; Mean age (SD) years = 23.0	Public speaking, serial addition task	No significant differences in: age, sex, education, cognitive ability. All middle class.	The high risk (FH+ and low sociability) group had significantly lower cortisol and HR stress responses than the low risk (FH- and

	(0.36) ; 61% female No family history of alcoholics over two generations (FH-): N = 95; Mean age (SD) years = 24.0 (0.38); 49% female			high sociability) group.
Substance abuse				
Moss, Vanyukov, & Martin, 1995	N = 184 High risk group, fathers with a diagnosis of a substance dependence disorder: N = 81; Mean age (SD) years = 10.86 (0.11) Low risk group, fathers had no history of a substance dependence disorder or any other psychiatric illness: N = 103; Mean age (SD) years = 11.1 (0.08) 100% male	Anticipation of an auditory event-related potential procedure	No differences in age, education, or psychiatric disorders	Those with a family history had significantly lower cortisol response in anticipation of the stress task.
Moss, Vanyukov, Yao, & Kirllova, 1999	N = 300 High risk group, fathers with a diagnosis of a substance dependence disorder: N = 118; Mean age (SD) years = 10.91 (0.90) Low risk group, fathers had no history of a substance dependence disorder or any other psychiatric illness: N = 182; Mean age (SD) years = 11.02 (0.06) 100% male	Anticipation of an auditory event-related potential procedure	No differences in age	The high risk group had significantly lower cortisol concentrations during the stress task than controls. Blunted cortisol responses to stress predicted uptake of tobacco and marijuana 4 years later.

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Chapter 2

Preliminary Evidence that Exercise Dependence is Associated with Blunted Cardiac and Cortisol Reactions to Acute Psychological Stress

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Abstract

Low or blunted cardiovascular and cortisol reactions to acute psychological stress have been shown to characterise those with a tobacco or alcohol dependency. The present study tested the hypothesis that exercise dependency would be similarly associated with blunted reactivity. Young female exercisers ($N = 219$) were screened by questionnaire for exercise dependence. Ten women with probable exercise dependence and 10 non dependent controls were selected for laboratory stress testing. Cardiovascular activity and salivary cortisol were measured at rest and in response to a 10-min mental arithmetic stress task. The exercise dependent women showed blunted cardiac reactions to the stress task and blunted cortisol at 10, 20, and 30 minutes post stress exposure. These effects could not be accounted for in terms of group differences in stress task performance, nor could the cardiac effects be attributed to group differences in cardio-respiratory fitness. It would seem that low stress reactivity is characteristic of a wide range of dependencies, and is not confined to substance dependence. Our results offer further support for the hypothesis that blunted stress reactivity may be a peripheral marker of a central motivational dysregulation.

Key words: Acute stress; Blood pressure; Exercise dependence; Heart rate; Salivary cortisol

The reactivity hypothesis contends that large magnitude cardiovascular reactions to acute psychological stress play a role in the development of cardiovascular pathology. Evidence in support comes from a number of large scale cross-sectional and prospective observational studies that attest to positive associations between the magnitude of cardiovascular reactions to acute psychological stress tasks and future blood pressure status (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll et al., 2001; Everson, Kaplan, Goldberg, & Salonen, 1996; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999; Treiber, Turner, Davis, & Strong, 1997), markers of systemic atherosclerosis (Barnett, Spence, Manuck, & Jennings, 1997; Everson et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews et al., 1998), and left ventricular mass and/or hypertrophy of the heart (Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Kapuku et al., 1999; Murdison et al., 1998). All of these outcomes are predictors of mortality and suggest that large cardiovascular reactions to acute stress are implicated in the development of cardiovascular inflammatory disease.

However, in the understandable enthusiasm to characterise the circumstances and antecedents of excessive reactivity and its consequences for health, the other end of the continuum has been largely neglected. The rarely articulated but implicit assumption is that low physiological reactivity in the face of acute psychological challenge is the more adaptive response, with no negative consequences for health or behaviour, i.e., low reactivity is benign or even protective. This assumption has recently been subject to challenge (Carroll, Lovallo, Phillips, 2009; Carroll, Phillips, & Lovallo, 2011). Low or blunted cardiovascular reactivity has been reported in epidemiological analyses to be associated with obesity and symptoms of depression cross-sectionally, as well as with an

increased risk of becoming obese and developing symptoms of depression five years later (Carroll, Philips, & Der, 2008; Carroll, Phillips, Hunt, & Der, 2007; Phillips, Hunt, Der, & Carroll, 2011). Analogously, blunted cortisol reactions to acute laboratory stress would seem to characterise patients with atopic dermatitis (Buske-Kirschbaum & Hellhammer, 2003).

Perhaps the most compelling evidence, to date, comes from studies of reactivity and tobacco and alcohol dependence. There is emerging evidence that low or blunted cardiovascular or cortisol reactivity is characteristic of those with substance dependencies and may indeed be a general marker for risk of addiction (Lovallo, 2006). Habitual smokers, for example, have been found to show diminished salivary and plasma cortisol (al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Kirschbaum, Scherer, & Strasburger, 1994; Kirschbaum, Strasburger, & Langkrar, 1993; Rohleder & Kirschbaum, 2006) and cardiovascular (Girdler, Jamner, Jarvik, Soles, & Shapiro, 1997; Phillips, Der, Hunt & Carroll, 2009; Roy, Steptoe, & Kirschbaum, 1994; Sheffield, Smith, Carroll, Shipley, & Marmot, 1997; Straneva, Hinderliter, Wells, Lenahan, & Girdler, 2000) reactions to acute psychological stress. It is unlikely that these effects reflect temporary abstinence during stress testing and its effects on stress task engagement (Roy et al., 1994). Blunted cardiovascular reactivity has been observed in female smokers regardless of whether they were wearing a nicotine replacement patch or not (Girdler et al., 1997). In addition, cardiovascular and cortisol reactivity has been compared among non smokers, smokers who abstained from smoking, and smokers who continued to smoke at their usual rate; smokers, irrespective of their assigned condition, showed blunted cardiovascular and cortisol reactions to acute stress (al'Absi et al., 2003).

Those addicted to alcohol have also been found to exhibit blunted cardiovascular and cortisol stress reactivity (Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002). In addition, relatively low reactivity would appear to be a characteristic of non alcoholics with a family history of alcoholism. In the Oklahoma Family Health Patterns project, young adults with a positive family history, particularly those with low sociability scores, showed lower cortisol and cardiac reactions to psychological stress than those with a negative family history of alcoholism and high sociability scores (Sorocco, Lovallo, Vincent, & Collins, 2006). Other studies of the offspring of parents addicted to alcohol or drugs provide further evidence; in a prospective study, boys with a positive family history who showed a blunted cortisol response to stress were more likely to experiment with cigarettes and marijuana (Moss, Vanyukov, Yao, & Kirillova, 1999). These data suggest that blunted reactivity may not only be a characteristic of those with a dependency, it may actually pre-date the dependency and signal risk of future addiction.

If low cardiovascular and cortisol reactivity is a marker of motivational dysregulation and linked to inherited risk of addictions (Lovallo, 2006), this should be evident with other dependencies. Although somewhat controversial, it has been argued that exercising has the potential to become an all consuming and damaging obsession (Morgan, 1979). The reported characteristics of what has come to be called exercise dependence resonate with those that typify substance addiction: experience of withdrawal symptoms on cessation of exercise; increasing tolerance; disturbed psychological functioning; exercising despite medical contraindications; interference with relationships or work (Bamber, Cockerill, & Carroll, 2000; Bamber, Cockerill, Rodgers, & Carroll, 2003; Robbins, 1985; Yates, 1983). Indeed, diagnostic criteria, not too dissimilar to those that define substance addiction, have

been proposed (Bamber et al., 2003). Accordingly, exercise dependence should provide an interesting model to test the contention that blunted stress reactivity is a marker of motivational dysregulation and is general feature of addiction and risk of addiction, including non substance dependencies. In the present study we compared the cardiovascular and cortisol reactions to acute psychological stress of individuals who were seemingly exercise dependent and those who were clearly not. It was hypothesised that the former would show blunted stress reactivity.

Methods

Participants

Questionnaires measuring exercise dependence were administered to 219 young adult women who were recruited from sports clubs and exercise classes at the University of Birmingham. Only women were included in the study as exercise dependence is reasonable well characterised in women and is evidently rarer in men (Bamber et al., 2000; Bamber et al., 2003). The mean (SD) age of the women recruited was 19.8 (2.25) years and their mean body mass index (BMI) was 21.6 (2.39) kg/m². Ten participants who scored highest on the exercise dependence criteria (exercise dependent group) and 10 who scored lowest (non exercise dependent group) were selected to attend a laboratory session to measure cardiovascular and cortisol reactions to an acute psychological stress task. Age, BMI, and scores on the exercise dependence questionnaires for the two groups are presented in Table 2.1. The majority of these 20 participants (95%) indicated that they were “white”, with one describing herself as “Indian”. None smoked, and none had a history of cardiovascular disease, a current endocrine or immune disorder, an acute infection or another chronic illness, with the exception of one participant with asthma and one reporting Pfeiffer syndrome. The exercise dependent group included three runners,

two rowers, two soccer players, one swimmer, one cricketer, and one tri-athlete. The non dependent group comprised two gymnasts, one runner, one judoist, one rower, one walker, and four women whose predominant physical activity was undertaken at organised exercise classes. Participants were paid £10 for completing the stress testing session; all gave written informed consent and the study was approved by the appropriate ethics committee.

Questionnaires

Exercise attitudes and beliefs questionnaire (EABQ)

The EABQ is a questionnaire specifically designed for this study. The 12 items were generated from the diagnostic criteria of exercise dependence in women proposed by Bamber and her colleagues on the basis of a qualitative study of exercise attitudes and behaviour in 56 female exercisers (Bamber, Cockerill, Rodgers, & Carroll, 2003). The criteria that informed the items were: a) an extreme preoccupation with exercise such that it impairs functioning in the psychological, social, occupational, or physical domains; b) symptoms of withdrawal as evidenced by adverse reactions to the interruption of exercise or unsuccessful attempts at exercise control. An example of the former would be loss of friends as a result of unreliability due to exercise preoccupation. An example of the latter would be depressed mood and/or extreme irritability when unable to exercise. The items were scored on a 7-point Likert-type scale where 0 = definitely not to 6 = definitely yes. Accordingly, total scores could range from 0 to 72. In the present screening sample, the EABQ showed acceptable internal consistency, Cronbach's $\alpha = .88$. The EABQ is reproduced in full in the Appendix.

Exercise dependence questionnaire (EDQ).

The EDQ is designed to measure relationships between exercise dependence and eating disorders and distinguish between primary and secondary independence (Ogden, Veale, & Summers, 1997). It is a 29 item measure which is scored on a 1-7 point Likert scale calculating dependence based on eight subscales. High internal reliabilities (Cronbach's α) for each of the subscales have been reported: interference with family social life, $\alpha = 0.81$; positive reward, $\alpha = 0.80$; withdrawal symptoms, $\alpha = 0.80$; exercise for weight control, $\alpha = 0.78$; insight into a problem, $\alpha = 0.76$; exercise for social reasons, $\alpha = 0.75$; exercise for health reasons, $\alpha = 0.70$; stereotyped behaviour, $\alpha = 0.52$; total score, $\alpha = 0.84$ (Ogden, Veale, Summers, 1997). The internal reliability for the whole scale in the present screening sample was $\alpha = .88$. A score of ≥ 116 out of a possible 203 on the EDQ is considered the threshold for possible exercise dependence (Bamber, Cockerill, & Carroll, 2000). Scores on the EDQ correlated highly with those on the EABQ, $r(215) = .72, p < .001$.

Exercise beliefs questionnaire (EBQ)

The EBQ is a 21-item measure of beliefs about the consequences of not exercising. It has been validated against clinical measures of psychological distress. Example items are 'if I do not exercise my brain will become unhealthy' and 'if I do not exercise I will be sexually unattractive'. Each item is responded to by selecting a position on 100cm line anchored at I do not believe this thought at all = 0 and I am completely convinced this thought is true. The EBQ has four factors with the following reported internal and test-retest reliabilities: social desirability, $\alpha = 0.87, r = .76$; physical appearance, $\alpha = 0.83, r = 0.77$; mental and emotional functioning, $\alpha = 0.89, r = 0.70$; vulnerability to disease and ageing, $\alpha = 0.67, r = 0.67$ (Loumendis, 1998). For the purposes of the study only the full scale score was used

as an additional check on propriety of group allocation. The internal reliability in the present screening sample for the full EBQ scale was high, $\alpha = 0.94$.

Physical activity assessment and the estimation of cardio-respiratory fitness

Physical activity was measured using the scale from the Whitehall II study (Marmot et al., 1991). Participants were asked how much time they spent in activities of light, moderate, and vigorous exercise intensity (0, 1-2, 2-5, 6-8, 9-10, 11+ hours per week). Category scores (0, 1, 2, 3, 4, or 5), derived from the above were multiplied by a weighting of 1, 2, and 3 for light, moderate, and vigorous intensity exercise, respectively. To facilitate the estimation of cardio-respiratory fitness (Jurca et al., 2005), the final values generated from the questionnaire were categorised as physical activity levels 1-5, where 1 signifies inactivity and 5 indicates participation in brisk exercise for over 3 hours per week. These physical activity levels, 1, 2, 3, 4 and 5 were then assigned scores of 0.00, 0.32, 1.06, 1.76, and 3.03, respectively (Jurca et al., 2005). Cardio-respiratory fitness in METS was estimated using the following formula, $((\text{age} * .10) - ((\text{BMI}) * .17) - ((\text{resting heart rate}) * .03) + (\text{physical activity score}) + 18.07$ (Jurca et al., 2005).

SCOFF eating disorders questionnaire

Since exercise dependence and disordered eating behaviour are often co-morbid (Bamber, Cockerill, & Carroll, 2000), the SCOFF questionnaire (Morgan, Reid, & Lacey, 1999) was administered; it contains 5 items which screen for the existence of an eating disorder. The questions focus on the core features of anorexia and bulimia and positive answers to ≥ 2 questions indicate possible caseness. In a study of a clinical population and matched controls the SCOFF demonstrated 100% sensitivity and 87.5% specificity (Morgan, Reid, & Lacey, 1999). A more recent study conducted in a primary care setting identified the SCOFF as having a sensitivity of 84.6% and specificity of 89.6% (Mond, 2008).

Psychological stress task questionnaire

This is a 7-item questionnaire, administered immediately following the stress task exposure. It requires participants to rate to what extent they found the task to be difficult, stressful, exciting, confusing, engaging, and embarrassing, as well as how they thought they had performed. Responses were made on a 0 (not at all) to 6 (extremely) Likert-type scale.

Cardiovascular and salivary cortisol measurements

The laboratory session consisted of four periods: 10 min adaptation, 10 min baseline, 10 min stress task and 30 min recovery. During the laboratory session systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured discontinuously from the non dominant arm using a standard brachial artery cuff and a semi-automatic sphygmomanometer (Critikon Inc, Tampa, FL). During the formal 10-min baseline, cardiovascular measurements were made at 2, 4, and 6 min and a saliva sample initiated at the 7th min. Cardiovascular measurements were made at 2, 4, 6, and 8 min during the acute stress task and at the same time points during the recovery period (latter data not reported). Four stimulated saliva samples were obtained using salivettes. Samples were obtained at 10, 20 and 30 min following the stress task. Participants placed the salivette dental swab into their mouths and gently chewed for 2 min to collect saliva. The swab was returned to the salivette tube and stored in the fridge until the end of the laboratory session. Salivettes were then centrifuged at 4000 rpm for 5 min and the saliva was pipetted into eppendorfs which were stored at -20°C until assay. Salivary cortisol samples were analysed all in the same day in duplicate by ELISA (IBL International, Germany). This assay is based on the competition principle and microplate separation. An unknown amount of cortisol present in the sample and a fixed amount of cortisol conjugated with

horseradish peroxidase compete for the binding sites of antibodies coated on to wells.

After an hour the microplate is washed to stop the competition reaction. After addition of a substrate solution the concentration of cortisol is inversely proportional to the optical density measured at 450 nm. The mean intra-assay coefficient of variation was 9% and the inter-assay coefficient was < 10%.

Acute psychological stress task

Participants undertook an acute psychological stress task: the 10 min paced auditory serial addition test (PASAT). The PASAT has been shown previously to reliably perturb both the cardiovascular system and salivary cortisol (Phillips, Carroll, Hunt, & Der, 2006; Phillips, Der, Hunt, & Carroll, 2009; Ring, Burns, & Carroll, 2002). Participants were presented with a series of single digit numbers by compact disc and required in each case to add the present number to the number previously presented and call out the answer. The intervals between the numbers were 4.5s for the first 2 min and shortened by 0.5s every subsequent 2 min. An experimenter sitting directly adjacent to the participants obtrusively scored participants' answers. The task also involved elements of competition and social evaluation. A leader board was displayed in the laboratory of the top five scores and the participants were instructed to attempt to beat the displayed scores. Participants started with 1000 points and were deducted five points for every wrong answer. If they made an error or hesitated they received a brief burst of loud aversive noise. If they did not make any errors within each block of 10 numbers, they received the noise at a point during the last five numbers of every block. All participants received the same number, i.e. 21, noise bursts. They were also videotaped throughout the task and instructed to watch themselves live on a television screen directly in front of them throughout the task; they were informed that the tape would be assessed by "body language experts". In reality, no such

assessment was made. If attention drifted, participants were prompted by an experimenter to keep looking at the television screen.

Procedure

The exercise dependent group was formed from the 10 highest scorers on the EABQ who also had EDQ scores of ≥ 116 and the non dependent group from the 10 lowest EABQ scores who also had scores of ≤ 116 on the EDQ. They were all non smokers. These 20 participants then attended a laboratory session starting at either 15:00 or 16:30. They were required to abstain: from alcohol 12 h, vigorous exercise, caffeine 2 h and food 1 h before the session. During the adaptation phase, participants were seated and the blood pressure cuff attached. At the end of the baseline period the participants were read the instruction of the PASAT and completed a brief practice to ensure they understood the task. Participants completed the PASAT task ratings immediately after the task. The schedule of cardiovascular and salivary cortisol measures are indicated above.

Data reduction and analysis

For the cardiovascular data, averages of each period (baseline and task) were computed. To check that the task perturbed cardiovascular activity, repeated measures ANOVAs were performed. The analogous analysis for the cortisol data was by multivariate ANOVA. Initial analyses of group differences was by means of repeated measures ANOVAs, using the Greenhouse-Geisser correction. Reactivity was then calculated as average task minus average baseline for HR, SBP and DBP. Salivary cortisol reactivity was calculated separately for the 10, 20, and 30 min post task samples by subtracting the baseline concentration in each case. Reactivity data were analysed using univariate ANOVA. Throughout, partial η^2 is reported as an index of effect size. Univariate ANOVA was also used to test for group differences in age, BMI, estimated cardio-respiratory fitness, data

from the exercise dependence and attitudes questionnaires, the personality inventory, the stress task ratings, and stress task performance.

Results

Validating allocation to exercise dependent and non dependent groups

As would be expected, the exercise dependent group had significantly higher total scores than the non dependent group on the EABQ. They also scored significantly higher on the EDQ and all its subscales, as well as on the EBQ. Groups did not differ significantly in either age or BMI. The relevant statistics are displayed in Table 2.1. Few participants met the SCOFF criterion for an eating disorder: two in the exercise dependent group and none in the non dependent group.

Table 2.1. Characteristics of the exercise dependent and non dependent group

	Non dependent	Dependent			
	Mean (SD)	Mean (SD)	F(1, 18)	<i>p</i>	η^2
Age in years	19.0 (0.94)	19.2 (0.92)	0.23	.64	.013
BMI in kg/m ²	23.5 (4.93)	21.1 (2.48)	1.96	.18	.098
EABQ	1.3 (1.77)	48.6 (7.93)	338.70	< .001	.950
EDQ total score	69.6 (11.52)	145.3 (12.31)	201.58	< .001	.918
EDQ subscales					
Interference -social/family/work	13.8 (3.67)	27.1 (2.33)	93.37	< .001	.838
Positive reward	7.4 (2.50)	22.7 (2.95)	156.64	< .001	.897
Withdrawal symptoms	8.6 (3.03)	22.6 (3.37)	95.46	< .001	.841
Exercise for weight control	7.3 (3.34)	14.5 (3.14)	24.74	< .001	.579
Insight into problem	10.4 (2.37)	18.9 (4.33)	29.65	< .001	.622
Exercise for social reasons	10.0 (4.97)	16.8 (2.74)	14.37	.001	.444
Exercise for health reasons	6.8 (1.48)	13.2 (2.94)	37.93	< .001	.678
Stereotyped behaviour	5.3 (2.00)	9.5 (3.57)	10.54	.004	.369
EBQ total score	443.0 (226.77)	1204.0 (418.87)	25.53	< .001	.586

Physical activity and estimated cardio-respiratory fitness

There was a tendency for the exercise dependent group to register higher physical activity scores than the non dependent group; the respective mean (SD) activity scores were 2.8 (0.54) and 2.3 (0.66). However, this difference was not quite statistically significant $F(1,18) = 3.60, p = .074, \eta^2 = .167$. Nevertheless, the exercise dependent group, 13.3 (0.87) METS, had higher estimated cardio-respiratory fitness than the non dependent group, 12.2 (1.03) METS, $F(1,18) = 6.97, p = .017, \eta^2 = .279$.

Menstrual cycle phase and oral contraceptives

None were taking any prescribed medication with the exception of the contraceptive pill which 55% of participants reported taking (40% in the exercise dependent group and 70% of the non dependent group), although this was not significantly different, $\chi^2(1) = 1.81, p = .178$. Seven women reported being in the follicular phase of the menstrual cycle in exercise dependent group, compared to three in the non dependent group. However, the distribution of those in the follicular and luteal phases between groups was not significantly different, $\chi^2(1) = 3.20, p = .074$.

Stress task performance, and post task ratings

The exercise dependent group tended to perform better on the PASAT (675.0, SD = 29.06) than the non dependent group (601.5, SD = 29.06) but the difference was not statistically significant ($p = .09$). Groups did not differ on their ratings of how stressful or difficult the task was nor in the extent that it engaged them. Indeed, the only group difference to emerge from these analyses was in rated performance; the exercise dependent group (3.1, SD = 1.20) judged that they had performed significantly better than the non dependent group, (1.9, SD = 1.10), $F(1,18) = 5.02, p = .04, \eta^2 = .218$.

Cardiovascular reactions to acute psychological stress

Baseline and reactivity values for SBP, DBP and HR are displayed in Table 2.2. There were no significant differences between groups in cardiovascular activity at baseline, with one exception. The exercise dependent group had significantly lower baseline SBP (107.8, SD = 10.94) than the non dependent group (118.7, SD = 5.16), $F(1,18) = 8.12$, $p = .01$, $\eta^2 = .331$. As revealed by analyses of the difference between average baseline and average stress task levels, the PASAT reliably perturbed SBP, $F(1,19) = 37.16$, $p < .001$, $\eta^2 = .662$, DBP, $F(1,19) = 20.67$, $p < .001$, $\eta^2 = .521$, and HR, $F(1,19) = 39.92$, $p < .001$, $\eta^2 = .678$. Repeated measures ANOVA revealed a significant time effect, $F(2, 36) = 38.76$, $p < .001$, $\eta^2 = .680$ and a significant group \times time interaction for HR, $F(2, 36) = 3.80$, $p = .049$, $\eta^2 = .174$; this is illustrated in Figure 1. There was no group main effect. There were no group or group \times time interaction effects for SBP and DBP. As would be expected from the above, there was a significant difference in HR reactivity between groups, $F(1,18) = 5.12$, $p = .04$, $\eta^2 = .221$; the exercise dependent group exhibited significantly smaller HR reactions to the acute stress. There were no significant group differences in SBP or DBP reactivity.

Table 2.2. Baseline cardiovascular levels and cardiovascular reactivity for the exercise dependent and non dependent groups

	Non dependent		Dependent	
	Baseline	Reactivity	Baseline	Reactivity
SBP (mmHg)	118.7 (5.16)	8.1 (6.52)	107.9 (10.93)	9.8 (6.86)
DBP (mmHg)	71.5 (6.37)	5.7 (5.67)	67.03 (8.14)	6.0 (6.12)
HR (bpm)	73.7 (9.02)	15.5 (9.58)	67.6 (13.76)	7.9 (4.61)

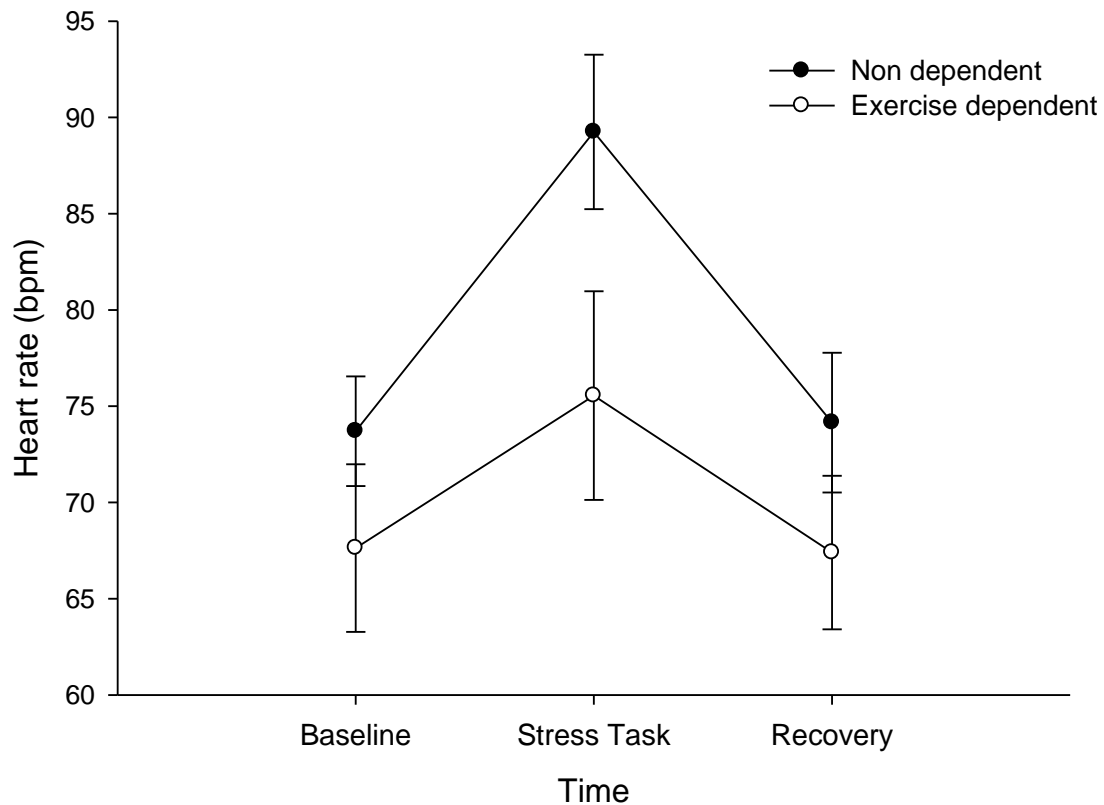


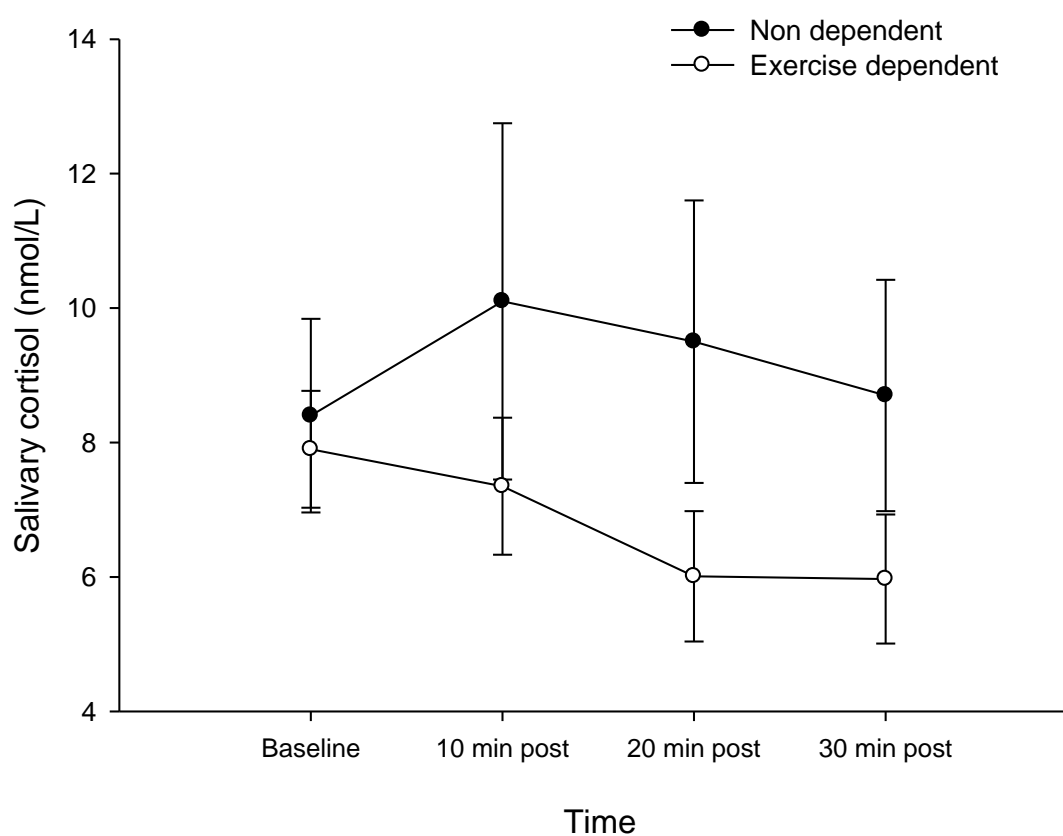
Figure 2.1. Mean (SE) HR activity at baseline and during and after the acute stress task in exercise dependent and non dependent women.

Salivary cortisol reactions to acute psychological stress

Repeated measures ANOVA revealed a significant effect of time, $F(3,54) = 3.53$, $p = .03$, $\eta^2 = .164$, and a group \times time interaction effect, $F(3,54) = 4.36$, $p = .01$, $\eta^2 = .195$. These effects are illustrated in Figure 2.2. In terms of cortisol reactivity, there were significant differences between groups at all three sampling points: for 10 min post task, $F(1,18) = 7.59$, $p = .01$, $\eta^2 = .297$; for 20 min post task, $F(1,18) = 7.06$, $p = .02$, $\eta^2 = .282$; for 30 min post task, $F(1,18) = 7.16$, $p = .02$, $\eta^2 = .285$. At each time point, the exercise dependent group showed blunted cortisol reactivity. Indeed, positive cortisol responses were apparent only for the non dependent group.

Table 2.3. Baseline cortisol levels and cortisol reactivity for the exercise dependent and non dependent groups

Cortisol (nmol/L)	Non dependent	Dependent
Baseline	8.4 (4.54)	7.9 (2.74)
Reactivity 10 mins post task	1.7 (2.33)	-.6 (1.12)
Reactivity 20 mins post task	1.1 (3.33)	-1.9 (1.43)
Reactivity 30 mins post task	.3 (2.23)	-2.0 (1.40)

**Figure 2.2.** Mean (SE) salivary cortisol at baseline and at 10 minutes, 20 minutes and 30 minutes post stress task in exercise dependent and non dependent women.

Sensitivity analyses

Given that cardio-respiratory fitness is negatively associated with cardiovascular reactivity (for a meta-analysis see Forcier et al., 2006) and that the groups differed on estimated fitness, the HR reactivity analysis was re-visited adjusting for estimated fitness in ANCOVA. The group difference in HR reactivity survived such adjustment, $F(1,17) = 6.76$, $p = .02$, $\eta^2 = .284$. Since there is no similarly compelling evidence that cardio-respiratory fitness affects cortisol stress reactivity (Sinyor, Schwartz, Peronnet, Brisson, & Seraganian, 1983) we did not adjust for fitness in our cortisol analysis. However, women in the luteal phase of the menstrual cycle have been shown to exhibit greater cortisol responses to acute stress than women in the follicular phase or women taking oral contraceptives (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999), we revisited the cortisol analysis adjusting for menstrual cycle phase and/or oral contraception. For this, we created a binary variable which contrasted those in the luteal phase not taking oral contraceptives with the rest of the sample. The observed group differences in cortisol reactivity at 10, 20 and 30 minutes post task remained significant after adjusting for menstrual cycle phase and oral contraception, $F(1,17) = 6.48$, $p = .02$, $\eta^2 = .276$, $F(1,17) = 6.11$, $p = .02$, $\eta^2 = .264$, $F(1,17) = 5.61$, $p = .03$, $\eta^2 = .248$, respectively.

There was also a tendency for the groups to differ on PASAT performance, which may signal variations in mental effort and commitment. Thus the main group analyses for HR and cortisol reactivity were repeated adjusting for performance. The effects reported above survived such adjustment: for HR reactivity, $F(1,17) = 6.36$, $p = .02$, $\eta^2 = .275$; for cortisol reactivity at 10 min post task, $F(1,17) = 9.62$, $p = .006$, $\eta^2 = .361$; for cortisol reactivity at 20 min, $F(1,17) = 7.09$, $p = .02$, $\eta^2 = .282$; and for cortisol reactivity at 30

min, $F(1,17) = 9.19$, $p = .008$, $\eta^2 = .351$. Largely similar outcomes emerged when we adjusted separately for perceived performance. Finally, excluding the two participants identified by the SCOFF as having a possible eating disorder also did not change the outcome: for HR reactivity, $F(1,16) = 5.42$, $p = .03$, $\eta^2 = .253$; for cortisol reactivity at 10 min post task, $F(1,16) = 8.54$, $p = .01$, $\eta^2 = .348$; for cortisol reactivity at 20 min, $F(1,16) = 6.51$, $p = .02$, $\eta^2 = .289$; or for cortisol reactivity at 30 min, $F(1,16) = 7.58$, $p = .01$, $\eta^2 = .322$.

Discussion

The results of the present study indicated that individuals identified as exercise dependent exhibited blunted cardiac and salivary cortisol reactions to acute psychological stress compared to their non dependent counterparts. Given that high cardio-respiratory fitness is associated with lower cardiovascular reactivity (Forcier et al., 2006), it was important to discount this as an alternative explanation for the present group differences in HR reactivity. We estimated cardio-respiratory fitness using an established algorithm (Jurca et al., 2005); the exercise dependent group were fitter than the non dependent group.

However, the group difference in HR reactivity remained significant when controlling for estimated fitness. In addition, the present effects could not be accounted for by group differences in objective and subjective stress task performance. Nor were they attributable to a co-morbid eating disorder. Only two exercise dependent participants were found to have a possible eating disorder and their exclusion did not materially change the outcomes.

This is the first evidence we know of that a non substance dependency is associated with blunted stress reactivity. However, our findings are very much in line with those from previous research showing that smokers are characterised by relatively blunted cardiovascular (Girdler et al., 1997; Phillips et al., 2009; Roy et al., 1994; Sheffield et al.,

1997; Straneva et al., 2000) and cortisol (al'Absi et al., 2003; Kirschbaum et al., 1994; Kirschbaum et al., 1993; Rohleder & Kirschbaum, 2006) reactivity. They also resonate with the findings from studies linking alcoholism (Lovallo et al., 2000; Panknin et al., 2002) and risk of alcohol dependence (Sorocco et al., 2006) with blunted cardiovascular and cortisol reactivity. The present results also offer further challenge to the assumption that low stress reactivity is necessarily benign (Carroll et al., 2009; Carroll et al., 2011).

More specifically, our findings lend further support to the hypothesis that blunted physiological reactivity may be a peripheral marker of central motivational dysregulation linked to inherited or acquired risk of a wide range of addictions (Lovallo, 2006). What might be the underlying neurophysiological mechanisms? We are some way from certainty but clues are emerging. The neural circuits that converge at the striatum and ventromedial prefrontal cortex would appear to shape the motivation of our behaviour, and these appear to be the same circuits that underlie the process of addiction. Neurochemical communication among these structures and among these areas change as experimental animals are exposed to increasing amounts of self-administered drugs of abuse (Koob, 2003), and recent research shows actual reconfiguration of neural connectivity in these areas following alcohol exposure (Xie et al., 2009). In short, these structures and their patterns of interaction may not only affect our physiology, but also our behaviour.

However, in the present context much of this remain highly speculative. As yet, nothing is known about the neurophysiology of exercise dependence and only human brain imaging studies will allow determination of whether or not substance and non substance dependencies have common circuitry and, accordingly, are just different manifestations of a general motivational dysregulation. However, given the preliminary nature of the present findings, replication in a larger sample is an essential first step.

The present study is not without its limitations. First, the sample is solely female which raises the issue of generalisation. However, as indicated, exercise dependence is much better characterised in women and would appear to be more prevalent (Bamber et al., 2000; Bamber et al., 2003). Second, the sample size is small. However, it represented the extremities of what is almost certainly a continuous distribution from problematic to non problematic exercise behaviour and was of the same order of magnitude as samples in some of the studies of reactivity and tobacco and alcohol addiction. Nevertheless, the modesty of the sample limits our capacity to control for multiple potential confounding variables. Accordingly, it remains possible that our findings are a product of confounding by some unmeasured variable (Christenfeld, 2004). However, we were able to discount stress task performance and perceptions, and our results could not be attributed to a co-morbid eating disorder in the exercise dependent. Further, the group differences in HR reactivity could not be accounted for by variations in cardio-respiratory fitness, although it should be conceded that we relied on an estimation of fitness. The group differences in cortisol reactivity could not be accounted for by variations in menstrual cycle phase and/or oral contraceptive use. Finally, it should be conceded that the cortisol reactions were modest and only evident in the non dependent group. Therefore in retrospect, the stress task may not have been optimal to adequately stimulate the hypothalamus-pituitary-adrenal axis.

In sum, like smoking and alcohol addiction, exercise dependence would appear to be characterised by blunted cardiac and cortisol reactions to acute psychological stress. This adds to the notion the low reactivity, far from being benign, may signify a state of central motivational dysregulation. The challenge for the future is to understand the neural

processes that may be common to different behavioural dependencies, as well as their influence on physiological reactions to psychological stress.

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Chapter 3

Disordered Eating Behaviour is Associated with Blunted Cortisol and Cardiovascular Reactions to Acute Psychological Stress

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Abstract

Research suggests a potential dysregulation of the stress response in individuals with bulimia nervosa. This study measured both cardiovascular and cortisol reactions to a standardised laboratory stress task in individuals identified as showing disordered eating behaviour to determine whether dysregulation of the stress response is characteristic of the two branches of the stress response system. Female students (N = 455) were screened using two validated eating disorder questionnaires. Twelve women with disordered eating, including self-induced vomiting, and 12 healthy controls were selected for laboratory stress testing. Salivary cortisol and cardiovascular activity, via Doppler imaging and semi-automatic blood pressure monitoring, were measured at resting baseline and during and after exposure to a 10-min mental arithmetic stress task. Compared to controls the disordered eating group showed blunted cortisol, cardiac output, heart rate, and stroke volume reactions to the acute stress, as well as an attenuated vasodilatory reaction. These effects could not be accounted for in terms of group differences in stress task performance, subjective task impact/engagement, age, BMI, neuroticism, cardio-respiratory fitness, or co-morbid exercise dependence. Our findings suggest that disordered eating is characterised by a dysregulation of the autonomic stress-response system. As such, they add further weight to the general contention that blunted stress reactivity is characteristic of a number of maladaptive behaviours and states.

Keywords: Acute psychological stress; Cardiovascular activity; Cortisol; Eating disorders

Stress plays a substantial role in disordered eating (Crowther & Chernyk, 1986; Lacey, Coker, & Birtchnell, 1986; Cattanach & Rodin, 1988; Koo-Loeb, Costello, Light, & Girdler, 2000). Disordered eating, particularly bulimia nervosa, is associated with increased negative perceptions of daily life stress and decreased coping skills (Crowther & Chernyk, 1986; Cattanach & Rodin, 1988; Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008). Increased perceptions of stress and negative affect can precede binges and ultimately contribute to the etiology and maintenance of bulimia nervosa (Abraham & Joseph, 1987; Cattanach, Malley, & Rodin, 1988; Cattanach & Rodin, 1988; Lingswiler, Crowther, & Stephens, 1989; Troop, Holbrey, Trowler, & Treasure, 1994). These behaviours suggest a potential dysregulation of the stress response in individuals with bulimia nervosa, which could contribute to the stress-illness relationship (Cattanach & Rodin, 1988; Koo-Loeb, Pedersen, & Girdler, 1998). Research measuring the neuroendocrine and cardiovascular responses to a standardised stress task in disordered eating individuals and healthy controls has an important part to play in determining whether bulimia is characterised by a general dysregulation of the autonomic stress response.

Few previous studies have used standardised laboratory procedures to investigate cardiovascular and neuroendocrine responses to stress in individuals with disordered eating; those that have produced conflicting results. In a study of hospitalised women with bulimia nervosa versus controls, women with bulimia had significantly blunted cortisol and norepinephrine stress reactions (Pirke, Platte, Laessle, Seidl, & Fichter, 1992). A broadly similar result emerged from a study examining reactions to two stress tasks in non-hospitalised women with bulimia and controls (Koo-Loeb et al., 1998); women with bulimia had blunted sympathetic activation in response to mental stress indicated by blunted systolic blood pressure, heart rate, and epinephrine reactions, and attenuated pre-

ejection period reactions. Two additional studies screened female students for disordered eating and stress-tested those with extreme high and low scores. Whereas one study observed no differences between those with disordered eating symptoms and controls in cardiovascular reactions to stress (Cattanach et al., 1988), the other reported that those high in disordered eating symptoms, but not meeting a clinical diagnosis for disordered eating, displayed higher heart rate and blood pressure reactivity compared to a group low in disordered eating symptoms (Koo-Loeb et al., 2000). A more recent study compared the stress reactivity of patients with bulimia nervosa, binge eating disorder, and obesity; although the groups did not vary on most measures of stress reactivity, those with bulimia were reported to show higher heart rate reactivity than the other groups (Messerli-Burgy, Engesser, Lemmenmeier, Steptoe, & Laederach-Hofmann, 2010).

There is no clear consensus emerging from these studies. Differences in previous findings may partially be attributed to the different populations of participants tested: in-patient hospitalised (Pirke et al., 1992), enrolled in an out-patient hospitalisation program (Messerli-Burgy et al., 2010), clinically confirmed diagnosis (Koo-Loeb et al., 1998), and high scores on an eating disorder questionnaire, but no official diagnosis (Cattanach et al., 1998; Koo-Loeb et al., 2000). It should be noted that in the three studies which tested confirmed bulimics, only two had a healthy control group and both showed blunted responses (Pirke, 1992; Koo-Loeb et al., 1998); the other study compared bulimics and people with binge eating disorder to an obese population (Messerli-Burgy et al., 2010).

The aim of the present study was to compare neuroendocrine, measured by salivary cortisol, and cardiovascular reactions to an acute psychological stress task in a group of participants who reported disordered eating behaviours versus healthy controls. On balance, it was hypothesised that those with disordered eating would show blunted

reactions to mental stress relative to controls, since blunted stress reactivity has been observed in two previous studies comparing bulimics to a healthy control group (Pirke et al., 1992; Koo-Loeb et al., 1998). To our knowledge, this is the first study to measure both cortisol and cardiovascular reactions to the same mental stress task in individuals with disordered eating behaviour. It is important to determine whether dysregulation of the stress response is characteristic of both branches, of the stress effector system: hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system. The one study, to date, to examine this issue measured cortisol and α -amylase, considered a marker of sympathetic nervous system activation (Chatterton, Vogelsong, Lu, & Ellman, 1996), to a standard laboratory stress exposure (Monteleone, Scognamiglio, Canestrelli, Serino, Monteleone, & Maj, 2011) in women with anorexia nervosa and bulimia. Relative to those with anorexia nervosa, women with bulimia showed blunted cortisol reactivity, whereas women with anorexia nervosa showed blunted α -amylase reactivity. In the present study, disordered eating and control groups were confirmed by responses to two questionnaires, one of which, the Eating Disorder Examination Questionnaire (Fairburn & Beglin, 1994), is regarded as an appropriate substitute for a clinical interview to diagnose eating disorders.

Methods

Participants

Questionnaires measuring problematic eating behaviour were administered to 455 female students (age, $M = 19.3$, $SD = 2.08$ years) recruited from University of Birmingham. Only women were targeted as problematic eating behaviour is reasonably well characterised in women and is rarer in men (Anderson, 1995; Woodside et al., 2001). The 12 participants who scored highest on the problematic eating criteria (disordered eating group; DE) and 12 who scored the lowest (healthy control group) were selected to attend a laboratory session

to measure cardiovascular and cortisol reactions to an acute psychological stress task. None smoked, and none had a history of cardiovascular disease, a current endocrine or immune disorder, an acute infection or another chronic illness, nor were any of the participants taking medication related to such disorders. However, one participant in the DE group was taking the antidepressant, fluoxetine. The outcome of the analyses with and without this participant were virtually identical and so it was decided to include them in the study. Means and standard deviations for age, body mass index (BMI), and estimated cardio-respiratory fitness for the two groups are presented in Table 3.1 and scores on eating disorder questionnaires are presented in Table 3.2. Participants were paid £10 for completing the laboratory session; all gave informed consent and the study was approved by the appropriate Ethics Committee.

Eating questionnaires

SCOFF

The SCOFF questionnaire contains 5 items which screen for the existence of an eating disorder. The questions focus on the core features of anorexia and bulimia and positive answers to ≥ 2 questions indicate possible caseness. In a study of a clinical population and matched controls the SCOFF demonstrated 100% sensitivity and 87.5% specificity (Morgan et al., 1999). A more recent study conducted in a primary care setting identified the SCOFF as having a sensitivity of 84.6% and specificity of 89.6% (Mond et al., 2008).

EDE-Q

The EDE-Q is a 36-item questionnaire version of the Eating Disorders Examination, screening device for symptoms of eating disorders (Fairburn & Beglin, 1994). The EDE-Q assesses frequency of eating disorder related behaviours over the past 28 days and is scored on a 7-point Likert scale. Participants are considered to be displaying symptoms of

an eating disorder if they register total scores ≥ 60 on items 1-15 and scores ≥ 32 on items 29-36 or if they reported self-induced vomiting. The EDE-Q sub-scales have shown good internal consistency, Cronbach's $\alpha = .84$, and a test-retest reliability of .86 (Stice & Bearman, 2001). In the present survey data, Cronbach's $\alpha = .92$ for items 1-15 and .93 for items 29-36.

Control and confounding variables

Exercise Dependence

The Exercise Attitudes and Beliefs Questionnaire (EABQ) was administered to control for the possible co-morbidity of exercise dependence and disordered eating (Davis et al., 1995, 1997; Epling & Pierce, 1988; Bamber, Cockerill, & Carroll, 2000). The EABQ is a 12-item questionnaire generated from the diagnostic criteria of exercise dependence in women proposed by Bamber and her colleagues on the basis of a qualitative study of exercise attitudes and behaviour in 56 female exercisers (Bamber, Cockerill, Rodgers, & Carroll, 2003). The items are scored on a 7-point Likert-type scale and the highest score is 72. The EABQ has been shown to show acceptable internal consistency, Cronbach's $\alpha = .88$ (Heaney et al., 2011).

Neuroticism

Neuroticism was measured by the Eysenck Personality Questionnaire Revised – Abbreviated (EPQR-A) (Francis et al., 1992). The subscale measure consists of six Yes/No questions in which each “Yes” scores one point, points are then added for a total score. The neuroticism subscale has demonstrated satisfactory levels of internal consistency Cronbach's $\alpha = .70-.77$ (Francis, Brown, & Philipchalk, 1992).

Physical activity and estimated cardio-respiratory fitness

Participants were asked to categorise their physical activity levels 1-5, where 1 signified inactivity and 5 indicated participation in a brisk exercise for over 3 hours per week. These physical activity levels, 1, 2, 3, 4, and 5 were then assigned scores of .00, .32, 1.06, and 3.03, respectively (Jurca et al., 2005). Cardio-respiratory fitness in METS was estimated using the following formula, $((\text{age}) \times 0.10) - ((\text{BMI}) \times 0.17) - ((\text{resting heart rate}) \times 0.03) + (\text{physical activity score}) + 18.07$ (Jurca et al., 2005).

Psychological stress task questionnaire

To test for potential group differences in perception of the stress task, participants were administered a 3-item questionnaire after repeating the stress task and asked to rate how they found the task in terms of whether the task was difficult, stressful, and engaging. Responses were made on Likert scale with 0 representing “not at all” and 6 representing “extremely.”

Salivary cortisol measurements

Two stimulated saliva samples were obtained using salivettes. Samples were obtained seven minutes into the baseline period and 20 min after the stress task exposure.

Participants placed the salivette dental swab in their mouths and gently chewed for 2 min to collect saliva. The swab was returned to the salivette tube and stored in the fridge until the end of the laboratory session. Salivettes were then centrifuged at 400 rpm for 5 min and the saliva was pipetted into eppendorfs which were stored at -20°C until assay.

Salivary cortisol samples were analysed all in the same day in duplicate by ELISA (IBL International, Germany). The mean intra-assay coefficient of variation was 10% and the inter-assay coefficient was <10%. Salivary cortisol assays were only analysed in 22 of the participants (11 in each group), due to insufficient saliva from the other two participants.

Cardiovascular measurements

The laboratory session consisted of four periods: 10 minutes adaptation, 10 minutes baseline, 10 minutes of stress task exposure, and 20 minutes of recovery. During the latter three periods, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured discontinuously using a semi-automatic sphygmomanometer (Critkon Inc, Tampa, FL), and heart rate (HR) was measured continuously by electrocardiography (ECG) with spot electrodes placed on the lower left rib and the right and left clavicle. Echocardiograph measurements were performed using a Philips Sonos 7500 ultrasound machine with an S3 two-dimensional transducer (1-3 MHz) and digital images of spectral waveforms were recorded continuously for later analysis. For each measurement point, averages were obtained from three or more spectral waveforms recorded; measurements for aortic blood flow to be averaged across 60-s intervals. An apical five-chamber view of the heart was used with Doppler mode to identify flow through the aortic valve during systole. The velocity profile of the aortic flow was obtained using pulse-wave spectral mode at a screen sweep speed of 100mm.s^{-1} , Doppler sampling of the flow was taken immediately below the orifice of the aortic valve. The flow was quantified automatically using the velocity time integral, which is the mean distance through which blood travels in the outflow tract during ventricular contraction. Each velocity time integral was made from at least three velocity profiles taken towards the end of expiration. The diameter of the aortic valve was measured from a parasternal long axis view and the aortic valve area was calculated. Stroke volume (SV) was calculated from velocity time integral x the aortic valve area; cardiac output (CO) was calculated as $\text{HR} \times \text{SV}$. Total peripheral resistance (TPR) was calculated as $(\text{MAP}/\text{CO}) \times 80$.

Acute psychological stress task

The psychological stress task was the paced auditory serial addition test (PASAT) (Gronwall, 1977), which demonstrates good test retest reliability (Willemssen et al., 1998) and reliably perturbs both the cardiovascular system and salivary cortisol (Ring, Burns, & Carroll, 2002; Phillips, Carroll, Burns, & Drayson, 2005; Phillips, Carroll, Hunt, & Der, 2006; Phillips, Der, Hunt, & Carroll, 2009b). The PASAT was presented via a compact disk player. Participants were presented with a series of single digit numbers and required, in each case, to add any given number to the number previously presented and call out the answer. Thus, the task involves attention and memory as well as simple addition. The intervals between the numbers were 4.5s for the first 2 min and shortened by .5 s every subsequent 2 min. The task also involved elements of competition and social evaluation. A leader board was displayed prominently and participants were informed that they were in direct competition with their peers. They were awarded 1000 points at the start of the task but lost five points for every wrong answer or omission. The final points total served as a performance score. They received a brief burst of loud, aversive noise at a point during the last five numbers of every block of 10 numbers, largely contingent on an error or a hesitation; all participants received the same number of noise bursts. Participants were also videotaped throughout and informed that the tape would be assessed by “body language experts.” In reality, no such assessment was made. Participants were also instructed to look at themselves in a mirror placed approximately .5 meters away and if their attention drifted, they were prompted by an experimenter to keep looking at the mirror.

Procedure

The DE group was formed from the 12 highest scorers on the SCOFF and Eating Disorder Examination Questionnaire (EDE-Q) and the control group was formed from the 12 lowest

scorers. All participants in the DE group reported self-induced vomiting. These 24 participants attended a laboratory session starting after 1430h. They were required to abstain: from alcohol 12 h, vigorous exercise 12 h, caffeine 2 h, and food and drink other than water 1 hour before testing. On entering the laboratory participants had their height and weight measured, and BMI was calculated. During the adaptation phase participants were asked to recline and had electrocardiograph electrodes and a blood pressure cuff attached, and a Doppler echocardiography probe positioned; they then sat quietly for 10 minutes. This was followed by a further formal 10-minute resting baseline period, after which participants were read instructions regarding the mental stress task and completed a brief practice to ensure they understood the task. Participants then completed the 10 minutes of stress task exposure, and immediately afterwards rated the task in terms of subjective impact. This was followed by a 20-minute recovery period. After the recovery period participants completed further questionnaires measuring potential confounding variables.

Data reduction and analysis

For the cardiovascular data, averages of each period (baseline, task, and recovery) were computed. Group differences in physical, personality, stress task performance, and post task ratings were explored using univariate ANOVAs. Analyses of group differences in cardiovascular activity were by means of repeated measures ANOVAs, using the Greenhouse-Geisser correction. Repeated measures ANCOVAs were used to test for group differences in salivary cortisol; assay batch and time of awakening served as covariates. It is important to adjust for time of awakening since the cortisol awakening response is strongly related to time of awakening (Stalder, Evans, Hucklebridge, & Clow, 2010) and may be related to DE (Therrien et al., 2008). ANCOVAs were also used to

determine if any group differences in reactivity withstood adjustment for potential confounders: i.e., other variables that differed between groups.

Results

Validating allocation to control and disordered eating groups

There were no differences between groups in age, height, weight, BMI, or estimated cardio-respiratory fitness. As indicated, the means and standard deviations of these characteristics are displayed in Table 3.1. As would be expected, the disordered eating group had significantly higher scores than the control group on the SCOFF and EDE-Q. The relevant statistics are presented in Table 3.2.

Table 3.1. Physical characteristics of the control and DE groups

	Control	DE
	Mean (SD)	Mean (SD)
Age (years)	19.5 (1.90)	19.8 (2.25)
Height (m)	1.7 (.07)	1.7 (.07)
Weight (kg)	61.0 (6.98)	64.7 (7.6)
BMI (kg/m ²)	22.2 (1.86)	22.6 (2.10)
Estimated cardio-respiratory fitness (METS)	18.3 (1.01)	18.6 (.97)
There were no significant differences between groups.		

Table 3.2. Eating behaviour characteristics of the control and DE groups

	Control	DE			
	Mean (SD)	Mean (SD)	F (1, 23)	p	η^2
SCOFF Total	0.0 (.00)	2.9 (.90)	125.94	< .001	.851
EDE-Q 1-15 Total	4.2 (3.7)	52.5 (17.78)	84.98	< .001	.794
EDE-Q 29-36 Total	0.1 (.29)	32.8 (13.34)	71.97	< .001	.768

Personality and co-morbidity characteristics

The disordered eating group registered higher scores on the questionnaire measure of exercise dependence (Control, $M = 20.0$, $SD = 11.58$; DE, $M = 36.3$, $SD = 16.5$), $F(1,23) = 7.87$, $p = .01$, $\eta^2 = .263$, which is often co-morbid with disordered eating (Bamber et al., 2000). There were no significant differences between groups for neuroticism ($p = .13$; Control, $M = 5.3$, $SD = 3.34$; DE = 7.7, $SD = 1.10$).

Menstrual cycle phase and oral contraceptives

Forty-two percent of participants reported taking the contraceptive pill (42% of the disordered eating group and 42% of the control group). Four women reported being in the follicular phase of their menstrual cycle in the disordered eating group and four women reported being in the follicular phase of their menstrual cycle in the control group. There were no differences between groups in either contraceptive pill uses or menstrual cycle phase.

Stress task performance and post task ratings

There was no significant difference between performance on the PASAT ($p = .78$). Groups did not differ on their ratings of how difficult ($p = .31$) or stressful ($p = .49$) the task was, nor in the extent to which it engaged them ($p = .29$). Means and standard deviations for groups on stress task performance and post task ratings are displayed in Table 3.3.

Table 3.3. Task performance and reported task impact for the control and DE groups

	Control	DE
	Mean (SD)	Mean (SD)
PASAT total score	700.4 (89.99)	685.4 (156.02)
Difficulty	3.7 (.65)	4.2 (1.27)
Stressful	4.3 (.90)	4.0 (.95)
Engaging	3.5 (.93)	4.0 (1.41)

There were no significant differences between groups.

Cardiovascular reactions to acute psychological stress

A repeated measures ANOVA on CO revealed a significant main effect for time, $F(2, 44) = 73.5, p < .001, \eta^2 = .770$. There was no significant main effect for group, but there was a significant group x time interaction, $F(2, 44) = 10.35, p = .002, \eta^2 = .320$. This interaction is illustrated in Figure 3.1a, which reveals that the ED group showed a blunted CO response to the stress task. Repeated measures ANOVA for HR yielded a significant main effect for time, $F(2, 44) = 103.78, p < .001, \eta^2 = .825$, and a significant main effect of group, $F(1, 22) = 7.56, p = .01, \eta^2 = .256$. There was also a significant group x time interaction, $F(2, 44) = 5.13, p = .03, \eta^2 = .189$. As shown in Figure 3.1b, the ED group was less responsive to the stress task than the control group. For SV, there were no main effects but there was a significant group x time interaction effect, $F(2, 44) = 8.15, p = .001, \eta^2 = .270$, which is illustrated in Figure 3.1c. SV increased to the stress task only in the control group. For SBP, $F(2, 44) = 64.21, p < .001, \eta^2 = .745$ and DBP, $F(2, 44) = 40.30, p < .001, \eta^2 = .647$, there was only a main effect of time. These summary data are presented in Figures 3.2a and 3.2b, respectively. For TPR, there was a significant effect for time, $F(2, 44) = 18.90, p < .001, \eta^2 = .462$, and a significant group x time interaction for, $F(2, 44) = 6.430, p = .004, \eta^2 = .226$. As can be seen in Figure 3.2c, the ED group showed a blunted vasodilatory response.

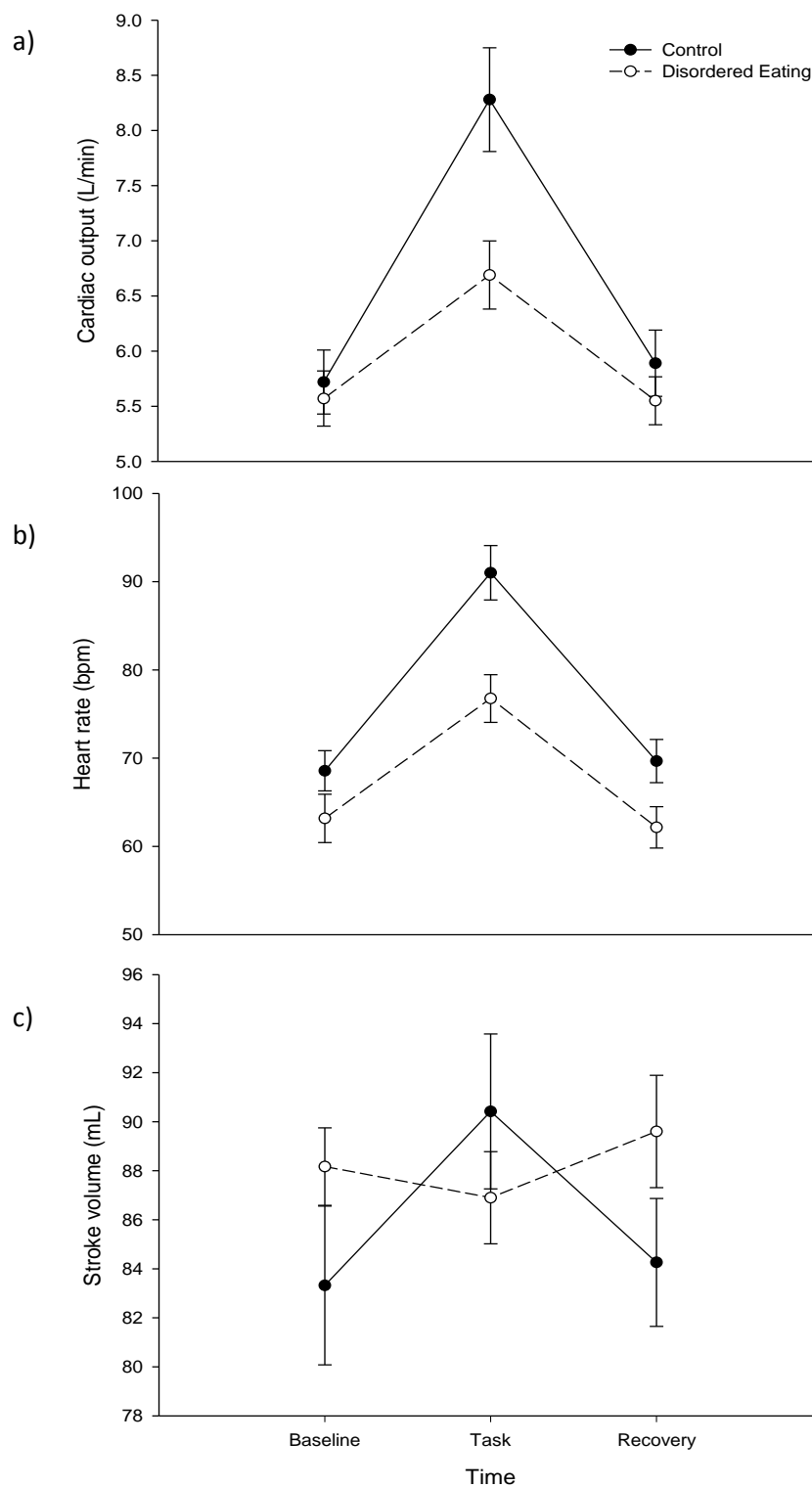


Figure 3.1. **a)** Mean (SE) cardiac output at baseline and during and after the acute stress task in the control and disordered eating groups. **b)** Mean (SE) heart rate at baseline and during and after the acute stress task in the control and disordered eating groups. **c)** Mean (SE) stroke volume at baseline and during and after the acute stress task in the control and disordered eating groups.

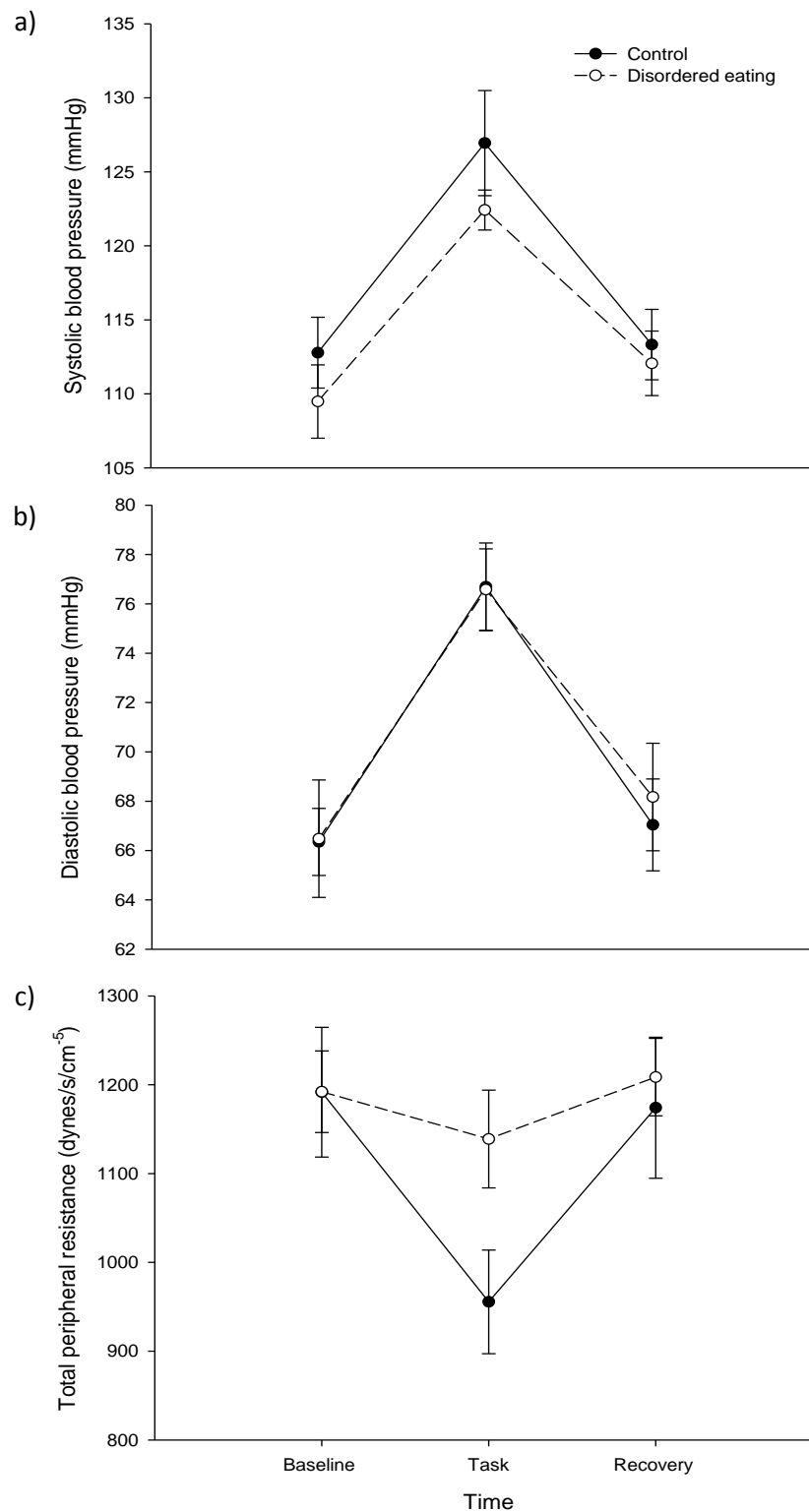


Figure 3.2. **a)** Mean (SE) systolic blood pressure at baseline and during and after the acute stress task in the control and disordered eating groups. **b)** Mean (SE) diastolic blood pressure at baseline and during and after the acute stress task in the control and disordered eating groups. **c)** Mean (SE) total peripheral resistance at baseline and during and after acute stress task in the control and disordered eating groups.

Salivary cortisol reactions to acute psychological stress

Repeated measures ANCOVA, adjusting for assay batch and awakening time, revealed a significant main effect of time, $F(1, 18) = 7.6, p = .01, \eta^2 = .297$, and a significant group \times time interaction, $F(1, 18) = 5.03, p = .04, \eta^2 = .218$. As shown in Figure 3.3, cortisol increased following the stress task only in the control group.

Covariance analyses

Given that exercise dependence has recently been found to be negatively associated with cardiac and cortisol reactivity (Heaney et al., 2011) and that the ED and control groups differed on their EABQ scores, the above analyses were re-visited adjusting for EABQ score in ANCOVA. The CO, $F(1, 44) = 7.66, p = .007, \eta^2 = .267$, and HR, $F(1, 44) = 4.08, p = .05, \eta^2 = .163$, group \times time interaction effects remained statistically significant, as did the interactions for SV, $F(1, 44) = 5.21, p = .01, \eta^2 = .199$, and TPR, $F(1, 44) = 3.73, p = .04, \eta^2 = .151$. Finally, the group \times time interaction effect for cortisol also withstood adjustment for exercise dependence score, $F(1, 44) = 4.61, p = .05, \eta^2 = .213$.

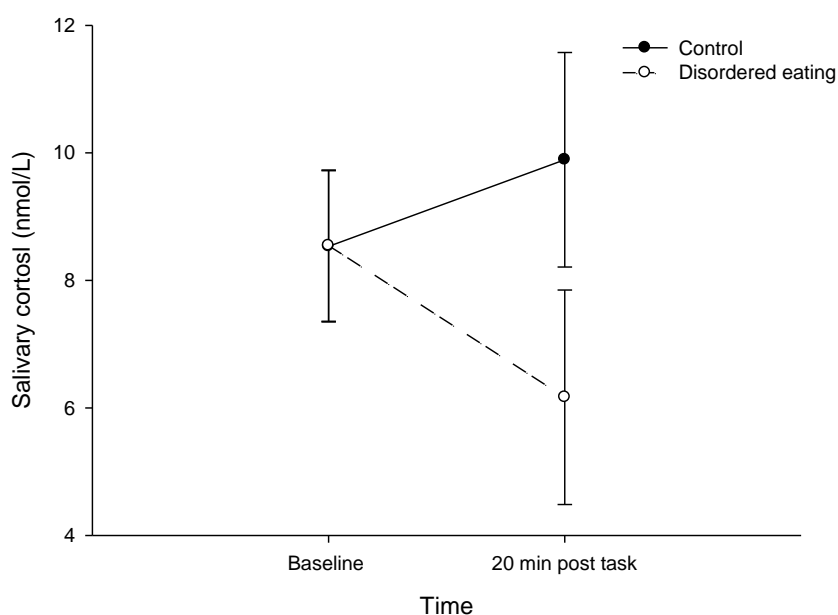


Figure 3.3. Mean (SE) salivary cortisol at baseline and at 20 minutes post stress task in the control and disordered eating groups.

Discussion

The present study compared neuroendocrine and cardiovascular reactions to an acute psychological stress task in a group of participants with disordered eating behaviours and healthy controls. The results were in line with our original hypothesis; individuals with disordered eating exhibited blunted salivary cortisol, CO, HR, and SV reactions and an attenuated vasodilatory response to acute psychological stress compared to healthy controls. There were no differences between groups in SBP and DBP reactivity. Given that exercise dependence has also been associated with blunted cardiovascular and cortisol reactivity (Heaney, Ginty, Carroll, & Phillips, 2011) and is often co-morbid with eating disorders (Davis et al., 1995; 1997; Bamber et al., 2000), it was important to adjust for EABQ scores as a potential confounder. All group x time interactions remained statistically significant when adjusting for EABQ scores. In addition, the present effects cannot be readily attributed to group differences in stress task performance and subjective task impact or task engagement, menstrual cycle phase, oral contraceptive use, neuroticism, age, BMI, or estimated cardio-respiratory fitness.

This is the first study we know of to measure both neuroendocrine and cardiovascular responses to the same mental stress task in individuals with disordered eating behaviour. Our results confirm previous findings of blunted cortisol (Pirke et al., 1992) and blunted cardiovascular (Koo-Loeb et al., 1998) reactions to acute mental stress tasks in women with bulimia nervosa. In the Koo-Loeb et al. (1998) study, group differences emerged for blood pressure, HR and the pre-ejection period, but not for SV, CO, or TPR. However, they used thoracic impedance cardiography and we used a relatively novel technology in this field, Doppler echocardiography, to measure cardiac activity. A recent study comparing measures of cardiac output and stroke volume using impedance cardiography and Doppler echocardiography concluded that the latter provided a more reliable and

clinically acceptable and accurate method of measuring cardiac activity during haemodynamic challenge (Fellahi et al., 2009). Such differences in sensitivity could go some way explaining why blunted cardiovascular reactivity was somewhat differently manifest in the two studies. In contrast, our results are seemingly at odds with those of another study that reported bulimics had relatively high heart rate reactivity (Messerli-Burgy et al., 2010). However, Messerli-Burgy and colleagues compared bulimics with a binge eating disorder group and a control group of obese individuals. There is evidence that obesity is also associated with blunted cardiovascular reactivity (Carroll et al., 2008), and so bulimics may only appear to show elevated cardiac reactivity when compared to controls who show blunted reactivity. It is worth noting that similar magnitude HR reactivity characterised their bulimic patients and our disordered eating individuals. In sum, it is difficult to draw firm conclusions about the relative reactivity status of bulimics in the absence of a healthy control group. Finally, the present results varied from those found in two previous studies examining individuals with high scores on eating disorder questionnaires (Cattanach et al., 1988; Koo-Loeb et al., 2000). This may have to do with the stringency of the selection criteria for extreme groups. In the present study, all 12 of the disordered eating disorder group met EDE-Q clinical criteria and all reported self-induced vomiting (Fairburn & Beglin, 1994).¹

The present results add further weight to the contention that individuals with disordered eating may have a dysregulated stress response (Cattanach & Rodin, 1988; Lo Sauro et al.,

¹ Using DSM-IV criteria for bulimia we created a numeric representation of the core symptoms of bulimia from the EDE-Q (American Psychiatric Association, 2000; Fairburn and Cooper, 1993). Higher scores represented more bulimic characteristics. There was a large difference between groups on the subscale; the means (SD) for the DE group was 19.2 (7.2) and for the control group 3.1 (4.1). Accordingly, although we did not have information on the diagnostic status of our selected DE participants, there is reason to believe that were all bulimic.

2008). The precise pattern of the present group differences, with the disordered eating group showing blunted cardiac reactivity and attenuated systemic vasodilatory reactions to stress, would seem to implicate β -adrenergic processes (Balanos et al., 2010). It is possible that the disordered eating behaviour is associated with diminished β -adrenergic activation. Alternatively, individuals vary in the sensitivity of β adrenergic receptors (Mills et al., 1994), and it is also possible that disordered eating is association with reduced receptor sensitivity. There is at least some evidence in favour of the former as bulimics have been found to show blunted norepinephrine reactions to stress (Pirke et al., 1992). The present results also implicate differences in HPA axis activation. The only previous study to examine both sympathetic and HPA axis activation found blunted cortisol stress reactivity in bulimic patients, but blunted α -amylase reactivity in patients with anorexia nervosa, suggesting some specificity in the two branches of the stress effector system (Monteleone et al., 2011). Others have proposed that sympathetic and HPA activation can be dissociated in some circumstances (Frankenhauser, 1982; Dickerson & Kemeny, 2004). However, there is also substantial evidence that they frequently covary, such that variations in the magnitude of the acute stress reactions of the sympathetic nervous system, as indexed by cardiac reactivity, predict subsequent variation in HPA reactions, as indexed by cortisol reactivity (Cacioppo, 1994; Al'Absi et al., 1997; Bosch et al., 2009). The present results suggest that disordered eating behaviour may be characterised by dysregulation in both branches of the stress response system.

The results of the present study offer further support for the hypothesis that blunted cortisol and cardiovascular reactivity may be a maladaptive response. Blunted cortisol and cardiovascular reactivity is characteristic of those with substance dependencies and may indeed be a general marker for risk of addiction (Lovallo, 2006). For example, habitual smokers have been found to show diminished salivary and plasma cortisol reactivity

(Kirschbaum, Scherer, Strasburger 1993; Kirschbaum, Scherer, Strasburger, 1994; al' Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Rohleder & Kirschbaum, 2006) and cardiovascular reactions (Girdler, Jamner, Jarvik, Soles, & Shapiro, 1997; Roy, Steptoe, & Kirschbaum, 1994; Phillips et al., 2009b) to a range of acute stress tasks, not attributable to temporary abstinence during a stress testing session (Girdler et al., 1997). Those addicted to alcohol have also been found to exhibit blunted cortisol and cardiovascular stress reactivity (Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002), as have the offspring of alcoholic parents (Moss, Vanyukov, Yao, & Krillova, 1999; Sorocco, Lovallo, Vincent, & Collins, 2006), suggesting that blunted reactivity may actually predict addiction and signal future risk of addiction. Blunted reactivity has also been associated with obesity (Carroll, Phillips, & Der, 2008), lower self-reported health (Phillips, Der, & Carroll, 2009a; de Rooij & Roseboom, 2010), and depression (Carroll, Phillips, Hunt, & Der, 2007; York et al., 2007; Salomon, Clift, Karlsdottir, & Rottenberg, 2009; de Rooij, Schene, Phillips & Roseboom, 2010). Most recently, blunted reactivity has been found in those reporting high perceived stress relative to their actual life events exposure (Ginty & Conklin, 2011) and in those with exercise dependence (Heaney et al., 2011). Although it may be premature to try to integrate these varied correlates of blunted reactivity, it is possible that they all reflect problems in motivation and emotion. Accordingly, it has been proposed that blunted physiological stress reactivity may be a peripheral marker of central motivational dysregulation (Carroll, Lovallo, & Phillips, 2009; Carroll, Phillips, & Lovallo, 2011). By central motivational dysregulation we mean the suboptimal functioning of those systems in the brain, converging at the striatum and ventromedial prefrontal cortex that appear to shape the motivation of our behaviour.

This study is not without limitations. First, the sample size is relatively small. However, it represented the extremities of what is almost certainly a continuous distribution from problematic to non problematic eating behaviour and was of the same order of magnitude of the studies of reactivity and eating disorders. Second, it remains possible that our findings are a product of a confounding by some unmeasured variable (Christenfeld, Sloan, Carroll, & Greenland, 2004). However, we were able to discount stress task performance and subjective task impact and engagement, BMI, cardio-respiratory fitness and age, nor could the group difference be attributed to co-morbid exercise dependence. Third, our sample was exclusively female which raises the issue of generalisation. However, as indicated, disordered eating is much better characterised in women and is decidedly more prevalent (Anderson, 1995; Woodside et al, 2001). Finally, participants did not have a formal diagnosis of an eating disorder, neither did we assess past history of eating disorders nor past or current treatment. Nevertheless, the EDE-Q has been proven to be as effective as clinical diagnosis interviews in identifying potential eating disorders (Fairburn & Beglin, 1994). Further, all our disordered eating participants reported, on two questionnaires, self-induced vomiting, and all met the criteria for an eating disorder on the SCOFF.

In conclusion, disordered eating was associated with a dysregulation of the autonomic stress-response, as evidenced by blunted cortisol and cardiovascular reactions to a standard mental stress task. The latter would appear to reflect reduced β -adrenergic activation. Our results, together with some, but not all, previous findings suggest that bulimia may indeed be characterised by suboptimal stress responses. Finally, the present data add further weight to the hypothesis that low reactivity may signify a state of central motivational dysregulation and may be characteristics of a number of maladaptive behaviours.

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Chapter 4

Cognitive Ability and Simple Reaction Time Predict Cardiac Reactivity in the West of Scotland Twenty-07 Study

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Abstract

Few studies have examined the association between cognitive ability and cardiovascular reactivity, although both have been implicated in later cardiovascular disease. We studied the relationship between cognitive ability, assessed using the Alice Heim-4 test of general intelligence, simple reaction time, and subsequent cardiovascular reactivity in 409 55-year-olds. Blood pressure and heart rate reactions to an acute mental arithmetic task were measured 7 years after cognitive assessment. In regression models that adjusted for baseline cardiovascular activity, socio-demographics, body mass index, medication status, and stress task performance, cognitive ability and reaction time were associated with future cardiac reactivity. Low reactivity was characteristic of those with relatively low cognitive ability. The results are consistent with the notion that high reactivity may not always be a maladaptive response.

Key words: Blood pressure; Cognitive ability; Heart Rate, Reactivity

Given that both low cognitive ability (Batty, Shipley, Mortensen, Gale, & Deary, 2008; Hart et al., 2003, 2004) and exaggerated cardiovascular reactions to acute stress exposure (Barnett, Spence, Manuck, & Jennings, 1997; Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll et al., 2001; Everson et al., 1997; Georgiades, Lemne, De Faire, Lindvall, & Fredrikson, 1997; Kapuku et al., 1999; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews et al., 1998; Matthews, Woodall, & Allen, 1993; Murdison et al., 1998; Newman, McGarvey, & Steele, 1999) have been implicated in cardiovascular disease, it is perhaps surprising that few studies have examined the association between cognitive ability and cardiovascular reactivity.

However, in a study of infants, greater suppression of a heart period based index of vagal tone during the cognitive challenge afforded by the Bayley Scale of Infant Development was associated with more mature cognitive skills and more coordinated motor behaviour (DeGangi, DiPietro, Greenspan, & Porges, 1991). A broadly similar outcome emerged from a more recent study of cardiovascular reactions to a task in which young adults were required to identify a target stimulus among a variety of distractor items (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009): R-wave to pulse interval, an index of sympathetic activity, was negatively associated with task performance, whereas respiratory sinus arrhythmia, an index of vagal tone, was positively related to performance. The authors interpret these outcomes as suggesting an association between enhanced sympathetic and reduced vagal cardiovascular influences and improved cognitive-attentional functioning. In contrast, no association between cardiovascular reactivity to memory tasks and task performance has been reported in studies of young adults (Bucks & Seljos, 1994) and the elderly (Wright, Kunz-Ebrecht, Iliffe, Foese, & Steptoe, 2005), although, in the latter study, superior memory performance was associated with faster

heart rate recovery following task exposure. Given the differences in the sample study, the physiological parameters measured, and the cognitive tasks employed, it is perhaps hardly surprising that no clear consensus emerges from these studies.

Further, with one exception (Wright et al., 2005), all of the studies were small scale ($N \leq 60$) and did not adjust for potential confounding variables. Perhaps more importantly, all of these previous studies measured cognitive ability as performance on the stress reactivity challenge. In our own research on reactivity to a mental arithmetic task in a substantial community sample, task performance was associated with cardiac reactivity such that good performance characterized those exhibiting high reactivity (e.g., Carroll, Phillips, & Der, 2008). However, tests of the association between cognitive ability and cardiovascular reactivity to mental stress would be better served by using measures of generic cognitive ability that are independent of the mental stress task employed to elicit reactivity.

Data from the West of Scotland Twenty-07 Study allowed us to examine the association between cognitive ability and cardiovascular reactivity using measures of cognitive ability that were independent of the mental stress task used and were taken at a different time. General cognitive ability and simple reaction time were measured at entry to the study and cardiovascular reactions to acute stress were assessed 7 years later. It is worth noting that simple reaction time has been found to correlate negatively with more traditional measures of general intelligence and indeed has been regarded *per se* as a measure of cognitive ability (Carlson & Jensen, 1982; Rabbitt, 1996). In addition, the richness of the West of Scotland dataset allowed adjustment for a substantial number of potential confounding variables. Based on the balance of previous evidence and recent research testifying to an association between low or blunted reactivity and a number of adverse health and

behavioural outcomes (Carroll, Lovallo, & Phillips, 2009; Carroll, Phillips, & Lovallo, 2011; Phillips, 2011) suggestive of impaired motivational regulation, it was hypothesized that relatively lower cognitive ability and slower reaction times would be associated with lower cardiovascular reactivity.

Methods

Participants

Data were collected as part of the West of Scotland Twenty-07 Study. Participants were from Glasgow and surrounding areas in Scotland, and have been followed up at regular intervals since the baseline survey in 1987 (Ford, Ecob, Hunt, Macintyre, & West, 1994). The study's principal aim was to investigate the processes that generate and maintain socio-demographic differences in health (Macintyre, 1987). Participants were chosen randomly with probability proportional to the overall population of the same age within a post code area (Ecob, 1987). Thus, this is a clustered random stratified sample. Three narrow age cohorts were chosen (aged 15, 35, and 55 years at entry). More complete details of the study are available elsewhere (Carroll et al., 2008; Phillips, Der, & Carroll, 2009).

The data reported here are from the oldest cohort and relate to the baseline survey during which cognitive ability, measured only in the oldest cohort, and simple reaction time were assessed and the third follow-up in 1994/5, during which cardiovascular reactions to an acute mental stress were measured. The mean (*SD*) temporal lag between sessions was 7.5 (0.27) years. Data were available for 409 participants. The sample was almost entirely Caucasian, reflecting the West-of-Scotland population from which it was drawn. Mean age (*SD*) at the baseline survey was 56.1 (0.61) years and at the third follow-up was 63.6 (0.60) years. There were 221 (54%) women and 188 (46%) men, with 224 (55%) from

manual and 182 (45%) from non-manual occupational households (occupational status data were missing for three participants). Mean (*SD*) body mass index, calculated from measured height and weight, was 26.3 (4.32) kg/m². The study was approved by the appropriate Ethics committee.

Apparatus and Procedure

In both testing sessions, participants were interviewed and tested in a quiet room in their homes by trained nurses. During the baseline survey, cognitive ability and simple reaction time were measured (Deary, Der, & Ford, 2001). Cognitive ability was assessed using part 1 of Alice Heim-4 (AH-4) test, a measure of general mental ability; administration and scoring were carried out as described in the test manual (Heim, 1970). The test consisted of 12 practice questions followed by 33 items measuring numerical reasoning ability and 32 items measuring verbal reasoning ability. The items are of increasing difficulty and measure individuals' ability to identify patterns and infer principles and rules. The test has been used in other population studies of individuals in the same age range (Rabbitt, Diggle, Smith, Holland, & McInnes, 2001; Singh-Manoux, Ferrie, Lynch, & Marmot, 2005) and scores on the AH-4 correlate well ($r=.66$) with other tests of general intelligence such as Raven's matrices (Heim, 1970). Simple reaction time was determined in milliseconds using a portal device originally designed for the UK Health and Lifestyle Survey (Cox et al., 1987). Participants rested the 2nd finger of their preferred hand on a key, which they were instructed to press as quickly as possible after 0 appeared on a small screen above. The location of the 0 was fixed throughout the task. Participants were given 8 practice trials and 20 test trials. The mean reaction time for these 20 trials served as an independent variable. The duration of practice afforded to participants was similar to most studies that relate reaction times to intelligence differences (Deary, 2000).

At the third follow-up, height and weight were measured and body mass index computed. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured by an Omron (model 705) sphygmomanometer (Omron Healthcare UK Ltd., West Sussex, UK). This semi-automatic blood pressure device is recommended by the European Society of Hypertension (O'Brien, Waeber, Parati, Staessen, & Myers, 2001). Following the interview, at least an hour, during which standard questions on antihypertensive medication status were asked, there was then a formal 5-min period of relaxed sitting, at the end of which a resting baseline reading of SBP, DBP, and HR was taken. They then undertook an acute psychological stress, the paced auditory serial addition test (PASAT), which has been shown in numerous studies to reliably perturb the cardiovascular system (Ring, Burns, & Carroll, 2002; Winzer et al., 1999) and to demonstrate good test-retest reliability (Willemssen et al., 1998). The task comprised a series of single digit numbers presented by audiotape and participants were requested to add sequential number pairs, at the same time retaining the second of the pair in memory for addition to the next number presented, and so on throughout the series. Answers were given orally and, if the participants faltered, they were instructed to recommence with the next number pair. The correctness of answers was recorded as a measure of performance. The first sequence of 30 numbers was presented at a rate of one every 4 s, and the second sequence of 30 numbers was presented at a rate of one every 2 s. The whole task took 3 min, 2 min for the slower sequence, and 1 min for the faster sequence. A brief practice was given to ensure that participants understood the requirements of the task. Only those who registered a score on the PASAT were included in the analyses. Of a possible score of 60, the mean (*SD*) score was 41.0 (9.04). Two further SBP, DBP, and HR readings were taken during the task, the first initiated 20 s into the task (during the slower sequence of numbers), and the second initiated 110 s later (at the same point during the faster

sequence). For all readings, the nurse ensured that the participant's elbow and forearm rested comfortably on a table at heart level. The two task readings were averaged, and the resting baseline value subsequently subtracted from the resultant average task value to yield reactivity measures for SBP, DBP, and HR for each participant. Household occupational group was classified as manual or non-manual from the occupation of the head of household, using the Registrar General's Classification of Occupations (1980). Head of household was usually the man.

Statistical Analysis

Differences in AH-4 scores and simple reaction time between sexes and household occupational groups were explored using analysis of variance (ANOVA). Repeated-measures ANOVAs, using baseline and task values, were undertaken to confirm that the PASAT perturbed cardiovascular activity, with η^2 used as a measure of effect size. The relationship between body mass index and AH-4 and simple reaction time and the relationship between total PASAT score and AH-4 and simple reaction time score were investigated by Pearson's correlation. Hierarchical linear regression analyses were used to determine whether AH-4 score and simple reaction time predicted cardiovascular reactivity 7.5 years later. Baseline cardiovascular values, which have been observed to covary with reactivity, were entered in Step 1. AH-4 and mean simple reaction time were entered in Step 2 in individual analyses. We then tested models in which, in addition to baseline, the following covariates were also entered: sex, household occupational status, body mass index, and whether or not participants were taking anti-hypertensive medication. Finally, regression analyses were undertaken, in which we additionally adjusted for performance scores on the PASAT. Given that the PASAT is also a measure of cognitive ability, this could be considered as over-adjustment. However, PASAT performance has been associated with reactivity in previous analyses of the West of

Scotland Study, as have all the other covariates above (Phillips, Hunt, Der, & Carroll, 2011; Carroll et al., 2000, 2003, 2008).

Results

Socio-Demographics, Body Mass Index, PASAT Performance, Cognitive Ability, and Simple Reaction Time

The overall mean (*SD*) AH-4 score was 29.3 (10.70) and mean (*SD*) simple reaction time was 342.5 (96.36) ms. The non-manual household occupational group registered substantially higher AH-4 scores than the manual occupational group, $F(1,406)=100.96$, $p<.001$, $\eta^2=.200$, as well as much faster reaction times $F(1,402)=16.48$, $p<.001$, $\eta^2=.040$. There were no significant sex differences for AH-4 score or simple reaction time. The summary statistics are reported in Table 4.1. Neither cognitive ability nor simple reaction time correlated with body mass index. AH-4 score and simple reaction time were negatively associated, $r(402)=-.25$, $p<.001$. AH-4 score, $r(406)=.43$, $p<.001$, and simple reaction time, $r(402)=-.14$, $p=.005$, were moderately correlated with PASAT performance score.

Table 4.1. Mean (SD) AH-4 Score and Simple Reaction Time by Sex and Occupational Status

	N	AH-4 Score (mean \pm SD)	Simple RT (ms) (mean \pm SD)
Sex			
Male	221	30.0 \pm 10.91	345.3 \pm 104.72
Female	187	28.5 \pm 10.64	340.3 \pm 88.85
Occupational group			
Manual	188	24.82 \pm 9.32	360.2 \pm 100.56
Non-manual	220	34.51 \pm 10.06	321.54 \pm 87.18

Cardiovascular Reactions to Acute Stress

Two-way (baseline \times task) repeated measures ANOVA indicated that, on average, the PASAT significantly increased cardiovascular activity: for SBP, $F(1,407)=311.13$, $p<.001$, $\eta^2=.764$, for DBP, $F(1,407)=247.38$, $p<.001$, $\eta^2=.61$; for HR, $F(1,407)=244.82$, $p<.001$, $\eta^2=.601$. The mean baseline, stress task, and reactivity values are presented in Table 4.2.

Table 4.2. Mean (SD) SBP, DBP, and HR Baseline, During PASAT, and Reactivity.

	Baseline	During PASAT	Reactivity
Systolic blood pressure (mmHg)	144.0 \pm 21.80	156.4 \pm 22.93	12.3 \pm 14.12
Diastolic blood pressure (mmHg)	83.7 \pm 11.28	90.72 \pm 13.37	7.0 \pm 8.96
Heart rate (bpm)	65.9 \pm 9.95	71.95 \pm 11.24	6.1 \pm 7.82

AH-4 Scores, Simple Reaction Times, and Future Cardiovascular Reactivity

In the first model, adjusting only for resting baseline cardiovascular values, AH-4 scores positively predicted future HR and SBP reactivity, $\beta=.17$, $t=3.58$, $p<.001$, $\Delta R^2=.029$ and $\beta=.16$, $t=2.40$, $p=.02$, $\Delta R^2=.013$, respectively; individuals with poorer cognitive ability had lower HR and SBP reactivity 7.5 years later. AH-4 scores did not significantly predict DBP values ($p=.07$). Simple reaction time negatively predicted future HR reactivity, $\beta=-.13$, $t=2.64$, $p=.009$, $\Delta R^2=.016$ and SBP reactivity, $\beta=-.10$, $t=2.11$, $p=.04$, $\Delta R^2=.006$. Participants who responded more slowly showed lower cardiovascular reactivity. Simple reaction time did not predict DBP ($p=.85$).

In regression analyses that additionally adjusted for sex, household occupational status, body mass index, and whether or not participants were taking antihypertensive medication, AH-4 scores predicted HR reactivity, $\beta=.155$, $t=2.86$, $p=.004$, $\Delta R^2=.019$. However, the association between cognitive ability and SBP reactivity was no longer significant ($p=.10$).

Simple reaction time predicted both HR reactivity, $\beta = -.11$, $t = 2.23$, $p = .026$, $\Delta R^2 = .012$ and SBP reactivity, $\beta = -.10$, $t = 2.09$, $p = .037$, $\Delta R^2 = .010$. In a final model that additionally controlled for performance on the PASAT, AH-4 scores continued to predict HR reactivity, $\beta = .11$, $t = 1.96$, $p = .050$, $\Delta R^2 = .009$. This final regression model is shown in Table 4.3.

Table 4.3. Predictors of heart rate reactivity in the fully adjusted AH-4 score regression model.

	β	t	p	R^2
Step 1				
Baseline heart rate	-.199	4.04	<.001	
Total PASAT score	.139	2.82	.005	
Blood pressure medication status	-.509	1.21	.228	
Body mass index	-.106	2.16	.031	
Occupational group	-.087	1.76	.080	
Sex	.007	0.148	.882	.099
Step 2				
Total AH-4 score	.114	1.96	.05	.009

The association between AH-4 score and SBP reactivity was again not significant in this model ($p = .84$). The same held true for simple reaction time, which in this final model continued to predict HR reactivity, $\beta = -.10$, $t = 1.99$, $p = .047$, $\Delta R^2 = .009$, but not SBP reactivity ($p = .08$). The final model for simple reaction time and HR reactivity is displayed in Table 4.4. The associations between cognitive ability, simple reaction time, and HR reactivity are illustrated by plotting reactivity against tertiles of AH-4 scores, Figure 4.1, and reaction time values, Figure 4.2.

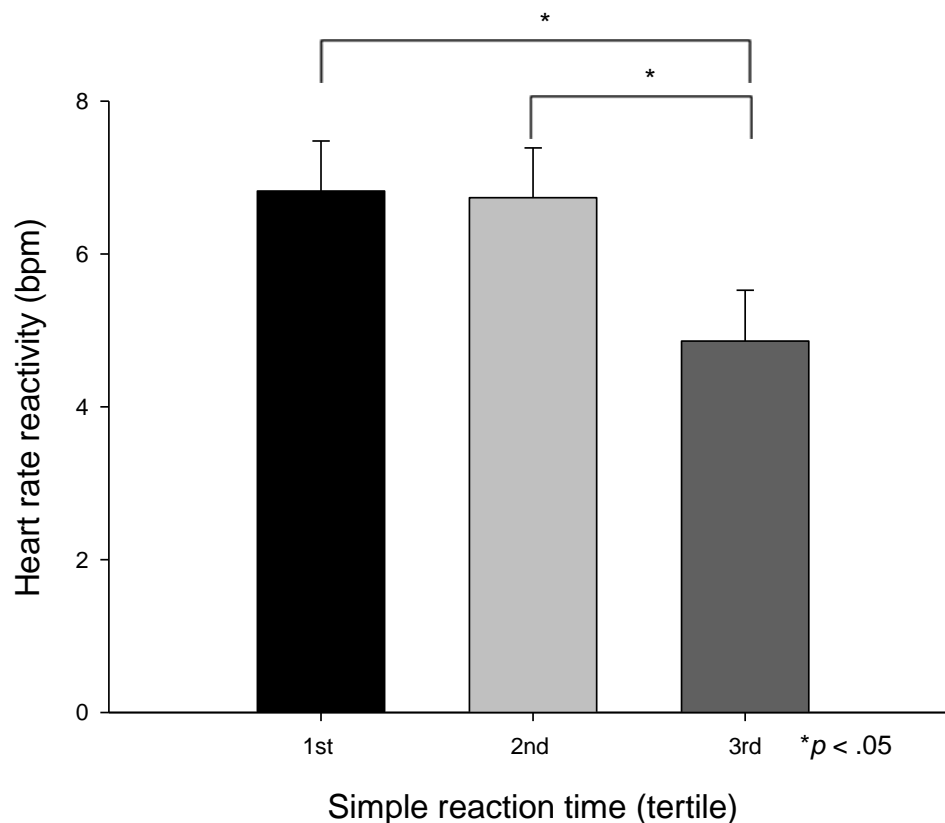


Figure 4.2. Heart rate reactivity (bpm) by tertiles of simple reaction time.

Discussion

This is the first study, as far as we are aware, to examine the prospective association between independent measures of cognitive ability and cardiovascular stress reactivity. Previous research has been cross-sectional and has used performance on the stress task as the measure of cognitive ability performance on the stress task. In the present study, low cognitive ability, as indexed by relatively poor AH-4 test scores and slow reaction times, was associated with relatively low cardiovascular reactivity. Whereas the associations with SBP reactivity were attenuated to non significance following full statistical adjustment, including PASAT performance score, the associations with HR reactivity remained significant. Thus, taking into account baseline HR, socio-demographics, body mass index, antihypertensive medication status, and performance score on the mental arithmetic stress task, cognitive ability continued to predict cardiac reactivity over seven years later. *Post*

hoc analyses of tertiles of cognitive ability indicated that it was those in the top third of intelligence test scores who registered the highest cardiac reactivity, whereas those with the slowest third of reaction time speeds had the lowest reactivity.

Accordingly, the direction of the association between cognitive ability and reactivity is in line with that observed in two earlier studies, which found that lower cardiovascular reactivity was associated with poorer performance on the mental stress task (DeGangi et al., 1991; Duschek et al., 2009). However, it should be conceded that two other studies including a sizable study in older adults failed to find an association between reactivity and cognitive ability as revealed by performance on the stress task (Bucks & Seljos, 1994; Wright et al., 2005). Nevertheless, the present study is the largest study by some considerable margin to address this issue. In addition, the direction of association observed in the present study is consistent with recent observations that low, not high, cardiovascular reactivity is associated with a range of adverse health and behavioural outcomes, such as obesity (Carroll et al., 2008), symptoms of depression (Carroll, Phillips, Hunt, & Der, 2007; Phillips et al., 2011; York et al., 2007), tobacco and alcohol dependence, as well as risk of dependence (al'Absi, 2006; al'Absi, Hatsukami, & Davis, 2005; Girdler, Jammer Jarvik, Soles, & Shapiro, 1997; Lovallo, Dickensheets, Myers, Thomas & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002; Phillips, Der, Hunt, & Carroll, 2009; Roy, Steptoe, & Kirschbaum, 1994).

An important distinction is made between cardiac and vascular reactivity in terms of both task and individual specificity (Kamarck, Jennings, Pogue-Geile, & Manuck, 1994). The most robust associations in the present study appeared for cognitive ability and cardiac reactivity. The associations for SBP reactivity did not withstand full adjustment for possible confounders, and there was no association whatsoever between cognitive ability

and DBP reactivity. Cardiac reactivity would appear to reflect both β -adrenergic and parasympathetic influences (Balanos et al., 2010; Sloan, Korten, & Myers, 1991). Thus, low cardiac reactivity could reflect reduced β -adrenergic drive or less of a reduction in vagal tone during the stress task. Regrettably, in the present study we cannot determine which of these was the predominant mechanism for low cardiac reactivity.

The present study is not without limitations. First, we measured only blood pressure and HR reactivity. It could have proved instructive to have a more comprehensive assessment of hemodynamics, such as that afforded by impedance cardiography. Further, a continuous rather than an intermittent (every 2 min) measure of blood pressure and HR would have allowed us to chart the time course of acute stress reactivity, as well as allowing us to represent cardiac reactivity as interbeat interval rather than HR. However, the decision to test participants in their own home and the size of the sample precluded more sophisticated measurement. Second, given the oral response mode in the PASAT, cardiovascular perturbations could be attributed to speech. However, similar levels of HR reaction to mental arithmetic with and without a speech component have been reported (Sloan et al., 1991), and we have reported substantial cardiovascular reactions to the PASAT when the mode of response was manual rather than oral (Balanos et al., 2010; Carroll, Phillips, & Balanos, 2009). Third, it should be acknowledged that the present effect sizes are small. However, our effects are of the same order as the positive associations between cardiovascular reactivity and future resting blood pressure in this sample (Carroll et al., 2003), as well as those observed in other prospective studies of reactivity and subsequent blood pressure status (Carroll et al., 1995, 2001; Markovitz et al., 1998; Matthews et al., 1993; Newman et al., 1999). Third, determining causality even in prospective observational studies is fraught with pitfalls (Christenfeld, Sloan, Carroll, & Greenland, 2004). Although we did adjust for a broad range of potential confounders, residual

confounding as a consequence of poorly measured or unmeasured variables cannot be wholly discounted.

In conclusion, indices of low cognitive ability were associated with low cardiac reactivity 7 years later. As such, our results are consistent with some, although not all, of the findings of previous much smaller-scale studies examining the association between cognition and reactivity. They are also consistent with recent evidence indicating that low reactivity is associated with a number of adverse health and behavioural outcomes and add weight to the notion that low reactivity can also be a maladaptive response to mental and behavioural challenges.

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Chapter 5

Cardiovascular and Cortisol Reactions to Acute Psychological Stress and Cognitive Ability in the Dutch Famine Birth Cohort Study

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Abstract

Given evidence linking blunted cardiovascular and cortisol reactions to acute stress and a range of adverse behavioural outcomes, the present study examined the associations between cardiovascular and cortisol reactivity and cognitive ability measured independently of the stress task exposure. Cognitive ability was assessed using the Alice Heim-4 test of general intelligence and two memory tasks in 724 men and women who were part of the Dutch Famine Birth Cohort Study. Blood pressure and heart rate, as well as cortisol reactivity, were measured to a battery of three standard acute stress tasks. Poorer cognitive ability was associated with lower cardiovascular reactions to stress and lower cortisol area under the curve. Our results are consistent with recent findings implicating low physiological stress reactivity in a range of adverse behavioural and health outcomes.

Key words: Blood pressure, Cognitive ability, Cortisol, Heart rate, Stress reactivity

The reactivity hypothesis proposes that large magnitude cardiovascular reactions to acute psychological stress contribute to the development of cardiovascular pathology. Evidence in support comes from a number of large-scale cross-sectional and prospective observational studies that show positive associations between the magnitude of cardiovascular reactions to acute psychological stress tasks and future blood pressure and hypertension status (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll et al., 2001; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999), markers of systemic atherosclerosis (Barnett, Spence, Manuck, & Jennings, 1997; Everson et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews et al., 1998), and left ventricular mass and/or hypertrophy of the heart (Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Kapuku et al., 1999; Murdison et al., 1998). Thus, the prevailing evidence implicates excessive cardiovascular reactivity in the development and expression of inflammatory cardiovascular disease.

There is now substantial evidence that hypertension is associated with poorer cognitive function (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Launer, Masaki, Petrovich, Foley, & Havlic, 1995; Singh-Manoux, Ferrie, Lynch, & Marmot, 2005; Waldstein, 2003), as well as evidence implicating systemic inflammation more generally in cognitive impairment. Little is known about the association between cardiovascular stress reactivity and cognitive function. If excessive reactivity contributes to inflammatory cardiovascular disease and inflammation is associated with poor cognitive function, we might expect reactivity to be negatively associated with cognitive ability; that is, higher cardiovascular reactivity would be related to poorer cognitive function.

Few previous studies have examined the association between reactivity and general cognitive ability. In a study of infants, greater suppression of a heart period based index of vagal tone during the cognitive challenge afforded by the Bayley Scales of Infant Development was associated with more mature cognitive skills and more coordinated motor behaviour (DeGangi, DiPietro, Greenspan, & Porges, 1991). A broadly similar outcome emerged from a more recent study of cardiovascular reactions to a task in which young adults were required to identify a target stimulus among a variety of distractor items (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009): R-wave to pulse interval, an index of sympathetic activity, was negatively associated with task performance, whereas respiratory sinus arrhythmia, an index of vagal tone, was positively related to performance. The authors interpret these outcomes as suggesting an association between enhanced sympathetic and reduced vagal cardiovascular influences and improved cognitive-attentional functioning. In contrast, no association between cardiovascular reactivity to memory tasks and task performance has been reported in studies of young (Bucks & Seljos, 1994) and older adults (Wright, Kunz-Ebrecht, Iliffe, Foese, & Steptoe, 2005), although in the latter study, superior memory performance was associated with faster heart rate recovery following task exposure. Given the variations in study samples, the physiological parameters measured, and the cognitive tasks employed, it is not surprising that no clear consensus emerges from these studies. With one exception (Wright et al., 2005), all of the studies were small scale and did not adjust for potential confounding variables. More importantly, all of these previous studies measured cognitive ability as performance on the stress reactivity challenge. Stronger tests of the association between cognitive ability and cardiovascular reactivity to mental stress would be afforded by using measures of cognitive ability that are independent of the mental stress task employed to elicit reactivity.

In only one published study to date was cognitive ability measured independently from mental stress task exposure (Ginty, Phillips, Der, Deary, & Carroll, 2011). Cognitive ability was assessed using the Alice Heim-4 test of general intelligence in 409 55-year-olds enrolled in the West of Scotland 20-07 Study. Blood pressure and heart rate reactions to an acute mental arithmetic stress task were measured 7 years later. Following statistical adjustment for a wide range of covariates including baseline cardiovascular activity, sociodemographics, body mass index, and medication status, cognitive ability and stress reactivity were positively associated. It was low cardiac reactivity that was characteristic of those with relatively low cognitive ability.

A number of studies have examined the relationship between cortisol reactivity and cognitive ability. However, there is no clear consensus regarding the direction of any association. One study reported that higher reactivity was associated with poorer cognitive performance (Wright et al., 2005), although another study observed the association only for men (Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001). However, the converse has also been observed; higher cortisol reactivity has been found to be associated with better memory performance (Domes, Heinrichs, Reichwald, & Hautzinger, 2002). Further, poorer declarative memory performance has been reported before and after a stressful task exposure for those who showed a smaller cortisol stress response (Lupien et al., 1997). High cortisol reactivity has also been observed to be related to better cognitive executive function (Blair, Granger, & Razza, 2005) and better dichotic listening performance (al'Absi, Hugdahl, & Lovallo, 2002). As far as we are aware, no substantial cohort study has examined the association between cortisol stress reactivity and cognitive ability.

The opportunity to readdress the issue of stress reactivity and cognitive ability is afforded by data from the Dutch Famine Birth Cohort Study (Painter et al., 2005; Ravelli et al., 1998). Cardiovascular and cortisol reactivity was measured to a battery of three stress tasks, and cognitive ability was assessed cross-sectionally, but independently, using the Alice Heim-4 test and, additionally, two memory tasks. The sample size was substantial, and the richness of the data set again allowed us to adjust statistically for a wide range of covariates. Based on the balance of previous evidence, including a recent substantial study finding a retrospective positive association between cardiac reactivity and cognitive ability, it was hypothesized that lower cardiovascular stress reactivity would be associated cross-sectionally with poorer cognitive ability. With regard to cortisol reactivity, we had no such clear expectations, given the variations in the findings of previous research.

Method

Participants

Participants were selected from the Dutch Famine Birth Cohort, which consists of 2414 men and women who were born in Amsterdam, the Netherlands, between November 1943 and February 1947. The selection procedures and subsequent loss to follow-up have been described in detail elsewhere (Painter et al., 2005; Ravelli et al., 1998). All 1423 members of the cohort who lived in the Netherlands on September 1, 2002 and whose current address was available were invited to the clinic to participate in a stress-testing session; a total of 740 attended. The study was approved by the local Medical Ethics Committee and carried out in accordance with the Declaration of Helsinki and the informed written consent of the participants.

General Study Parameters

Trained research nurses undertook anthropometric measurements and conducted a standardized interview in which information was obtained about socioeconomic status (SES), educational level, lifestyle, and use of medication. Height was measured twice using a fixed or portable stadiometer and weight was measured twice using Seca and portable Tefal scales. Body mass index (BMI) was computed as weight (kg)/height (m²) from the averages of the two height and weight measurements. SES was defined according to the International Socio-Economic Index (ISEI)-92, which is based on the participant's or their partner's occupation, whichever has the higher status (Bakker & Sieben, 1992). Values in the ISEI-92 scale ranged from 16 (low status) to 87. Participants were considered to consume alcohol if they drank at least one alcoholic beverage per week. Educational level was measured on a 10-point scale (1 = primary education not completed, 10 = university completed).

Cognitive Function

Cognitive function was assessed using the fourth version of the Alice Heim test (AH-4) (Heim, 1970) measuring general mental ability and a paragraph encoding and recall task measuring episodic memory. Participants were tested individually, and both tests were performed in the morning. The AH-4 is a measure of general mental ability (Deary, Der, & Ford, 2001), and was administered and scored as described in the test manual (Heim, 1970). The test comprises 12 practice questions followed by 33 items measuring numerical reasoning ability and 32 items measuring verbal reasoning ability. The test has been used in other population studies of individuals in the same age range (Rabbitt, Diggle, Smith, Holland, & McInnes, 2001; Singh-Manoux et al., 2005). Participants were given 10 min to answer as many items as possible, and the percentage of correct responses was taken as the AH-4 score. For the paragraph encoding (memory task part 1) and recall

test (memory task part 2), two paragraphs were orally presented (prerecorded on tape). Participants were told to remember as many story elements as possible and asked to reproduce the story immediately (part 1) and 30 min later (part 2). In each case, the number of correctly retrieved elements was recorded.

Psychological Stress Protocol

The stress protocol, which started in the afternoon between the hours of 12:00–14:00, approximately 1 h after a light lunch, lagged the cognitive assessment by mean (SD) 3 h and 11 min (50 min). It began with a 20-min baseline period after which three psychological stress tasks were performed: Stroop, mirror tracing, and a speech. Each stress task lasted 5 min, with 6 min in between and 30 min of recovery following the final stress task. The Stroop task consisted of a single-trial computerized version of the classic Stroop color–word conflict challenge. After a short introduction, participants were allowed to practice until they fully understood the requirements of the task. Errors and exceeding the response time limit of 5 s triggered a short auditory beep. For the mirror-tracing task, a star had to be traced that could only be seen in mirror image (Lafayette Instruments Corp., Lafayette, IN). Every divergence from the line triggered an auditory stimulus. They were allowed to practice one circuit of tracing. Participants were instructed to prioritize accuracy over speed and were told that most people could perform five circuits of the star without divergence from the line within the given 5 min. Prior to the speech task, participants listened to an audio-taped instruction in which they were told to imagine a situation in which they were falsely accused of pick pocketing. They were then given 2 min to prepare a 3-min speech in which they had to respond to the accusation. The speech was videotaped, and participants were told that the number of repetitions, eloquence, and persuasiveness of their performance would be assessed by a team of communication experts and psychologists. After completion of the stress protocol,

participants completed a 7-point rating scale of stress task impact, including participants' commitment to the tasks.

Continuous blood pressure (BP) and heart rate (HR) recordings were made using a Finometer or a Portapres Model-2 (Finapres Medical Systems, Amsterdam, the Netherlands). There were no differences in reactivity as a function of the two different measuring devices. Six periods of 5 min were designated as the key measurement periods: resting baseline (15 min into the baseline period), Stroop, mirror-tracing, speech task (including preparation time), recovery 1 (5 min after completing the speech task) and recovery 2 (25 min after completing the speech task). Mean systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR were calculated for each measuring period. A total of seven saliva samples were collected using Salivettes (Sarstedt, Rommelsdorf, Germany): at 5 and 20 min of the baseline period, at 6 min following completion of the Stroop task and the mirror tracing task, and at 10, 20, and 30 min after completion of the speech task. Salivary cortisol concentrations were measured using a time-resolved immunofluorescent assay (DELFI) (Wood, Kilpatrick, & Barnard, 1997). The assay had a lower detection limit of 0.4 nmol/l and an inter-assay variance of 9–11% and an intra-assay variance of less than 10%.

Statistical Analyses

Baseline cortisol was computed as the mean of the first and the second cortisol concentration measures during the baseline period. Cortisol reactivity was calculated as cortisol area under the curve (AUC) using the average baseline and the five subsequent measures, and applying the trapezoid method grounded to zero (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Because the distribution of AUC values was skewed, they were \log_{10} transformed for the purposes of analyses. Baseline cardiovascular

activity was the average of values recorded in the 5-min period 15 min into the baseline. BP and HR measures were averaged for each of the three stress tasks, and the highest 5-min average was used to determine peak stress reactivity. Cardiovascular stress reactivity was defined as the difference between these peak averages during stress and baseline for each of the three cardiovascular variables. The SES measure had eight missing values; we imputed these values using the SPSS linear trend at point method. The AH-4 score and cortisol had skewed distributions and are summarized with medians and interquartile ranges (IQR) and geometric means and standard deviations, respectively.

Differences in cognitive function scores between men and women and those from a lower and higher SES background were examined with Mann-Whitney (sex) and Kruskal-Wallis (SES) tests in the case of AH-4 score and t test (sex) and analysis of variance (ANOVA) (SES) in the case of memory scores. Correlations were calculated between AH-4 score (Spearman) and memory scores (Pearson) and general study parameters. Linear regression models were applied to analyse the associations between the cognitive function measures and baseline physiological activity and stress reactivity. Associations between cognitive function measures and baseline activity were adjusted for sex and SES. The stress reactivity regression models were first run without adjustment, then with adjustment for sex, SES, educational level, and age and, secondly, with additional adjustment for BMI, alcohol consumption, smoking, use of antihypertensive, antidepressant, and anxiolytic medication, commitment to the stress tasks, and baseline physiological activity. These covariates were selected as they have been shown to be directly or indirectly associated with reactivity in previous studies (Carroll, Phillips, & Der, 2008; Ginty et al., 2011; Lovallo, 2011; Phillips, Hunt, Der, & Carroll, 2011). In the case of cortisol AUC, because it was grounded to zero, baseline cortisol adjustments were made in all three of the cortisol AUC regression models for each of the cognitive ability measures. Differences were

considered to be statistically significant if p values were $\leq .05$. SPSS 16.0 (SPSS Inc., Chicago, IL) was used to perform the statistical analyses.

Results

Study Population

Of the 740 cohort members who participated in the study, 725 completed the psychological stress protocol. Fifteen persons were unable to participate in or finish the stress protocol due to logistical problems ($n = 5$) or because they were feeling unwell ($n = 10$). Due to technical problems, BP and HR recordings were unavailable for four individuals. A total of 270 participants had one or more missing cortisol values as a result of insufficient saliva, and were excluded from the cortisol analyses. A total of 724 participants had complete data on at least one of the two cognitive tests. Forty-seven percent ($n = 342$) of the study population was male; the mean age was 58.3 ± 0.9 years. The mean SES level was 49.7 ± 14.1 , and the mean educational level was 4.5 ± 2.2 . A total of 67.5% consumed at least one alcoholic beverage every week; 23.9% were smokers; 23.5% were using antihypertensive medication, and 12.0% were using antidepressant or anxiolytic medication.

Cognitive Function

The overall median AH-4 score was 72.4 ± 18.9 (IQR). The overall mean score on the first part of the memory task was 21.5 ± 6.9 and on the second part of the memory task was 17.9 ± 7.0 . Table 5.1 shows the results for the three measures of cognitive function according to sex and SES level. Men had a significantly higher AH-4 score than women ($p < .001$). Those from a higher SES background had a higher AH-4 score ($p < .001$), higher memory 1 ($p = .02$) and memory 2 ($p = .01$) scores compared to those from a lower SES background. AH-4 score was positively correlated with educational level

($r = .46, p < .001$) and negatively with alcohol consumption ($r = -.13, p = .001$) and smoking ($r = -.15, p < .001$). Memory score 1 and 2 were both positively correlated with educational level ($r = .29, p < .001$; $r = .30, p < .001$) and negatively with age ($r = -.12, p = .002$; $r = -.11, p = .01$), alcohol consumption ($r = -.09, p = .03$; $r = -.09, p = .04$) and smoking ($r = -.12, p = .003$; $r = -.14, p < .001$).

Table 5.1. Median (IQR) AH-4 and mean (SD) memory test (MT) scores by sex and socio-economic status

	<i>N</i>	AH-4 correct items (%)	MT score part 1	MT score part 2
Sex				
Male	342	75.8 (16.1)	21.6 (7.0)	18.2 (7.3)
Female	382	69.2 (21.4)	21.4 (6.8)	17.7 (6.7)
SES				
Low	344	67.9 (21.7)	20.5 (6.5)	16.9 (6.8)
High	380	75.4 (16.1)	22.3 (7.1)	18.8 (7.1)

MT = memory test; SES = socio-economic status

Reactivity

The psychological stress protocol significantly perturbed cardiovascular activity and cortisol (all $p < .001$). Table 5.2 shows that mean SBP reactivity was 47.6 ± 20.7 mmHg, DBP reactivity 21.4 ± 9.1 mmHg, HR reactivity 11.8 ± 9.5 bpm, and the geometric mean for cortisol AUC was 448.5 ± 1.8 .

Table 5.2. Mean (SD) cardiovascular and cortisol values for baseline, stress, and reactivity.

	<i>N</i>	Baseline	Stress	Reactivity
Systolic Blood Pressure (mmHg)	720	127.9 (21.0)	175.4 (28.8)	47.6 (20.7)
Diastolic Blood Pressure (mmHg)	720	65.9 (12.0)	87.2 (14.4)	21.4 (9.1)
Heart Rate (bpm)	720	74.3 (10.5)	86.0 (14.4)	11.8 (9.5)
Cortisol (nmol/l) *	455	4.4 (1.8)*	448.5 (1.8)**	

* Data are given as geometric means \pm SD. **AUC

In the subsequent cortisol AUC analyses, as indicated, we adjusted for baseline cortisol. Men and women did not differ in SBP, DBP, and HR stress reactivity, but women had lower cortisol reactivity ($p < .001$) compared to men. Those from a higher SES background had higher SBP ($p = .01$) and HR ($p < .001$) reactivity, and cortisol AUC ($p = .03$) than those from a lower SES background.

Educational level was positively correlated with SBP ($r = .14, p < .001$), HR ($r = .14, p < .001$). BMI was negatively correlated with HR reactivity ($r = -.20, p < .001$) and cortisol AUC ($r = -.11, p = .02$). Alcohol consumption was negatively correlated with HR reactivity ($r = -.11, p = .004$) and cortisol AUC ($r = -.11, p = .02$). Smoking was negatively correlated with SBP ($r = -.20, p = .002$), DBP ($r = -.09, p = .01$), HR ($r = -.19, p < .001$) reactivity, and cortisol AUC ($r = -.12, p = .01$). Use of antihypertensive medication was negatively correlated with HR reactivity ($r = -.08, p = .04$) and use of antidepressant or anxiolytic medication was negatively associated with SBP ($r = -.12, p = .002$) and DBP ($r = -.10, p = .01$) reactivity.

Cognitive Function and Baseline Cardiovascular and Cortisol Activity

Memory score 1 was negatively associated with baseline cortisol. Per unit increase in memory score 1, baseline cortisol increased 0.8 % ($p = 0.04$). There were no other significant associations between cognitive function and baseline cardiovascular and cortisol activity.

Cognitive Function and Cardiovascular and Cortisol Reactivity

AH-4 score, memory score 1, and memory score 2 were all significantly positively associated with SBP, DBP, and HR reactivity: the lower the reactivity the lower the cognitive ability. Effect sizes and other statistics of these associations are presented in Tables 5.3 (SBP reactivity), 5.4 (DBP reactivity), and 5.5 (HR reactivity). Tables 5.3, 5.4,

and 5.5 also show that, firstly, adjustment for sex, SES, educational level, and age and then, additionally, for BMI, alcohol consumption, smoking, use of antihypertensive medication, use of antidepressant or anxiolytic medication, commitment to the stress tasks, and baseline SBP/DBP/HR, did not abolish associations for SBP and HR, but did attenuate DBP findings to nonsignificance. Although effect sizes became somewhat smaller, in all cases the associations remained statistically significant. The associations are illustrated by plotting tertiles of cognitive ability scores against reactivity in Figures 5.1 (SBP reactivity), 5.2 (DBP reactivity), and 5.3 (HR reactivity).

Table 5.3. Regression models AH-4 and memory test scores and SBP reactivity.

	β	t	p	R ² change
AH-4 correct items				
Unadjusted	0.25	4.89	<.001	0.03
Model 1	0.21	3.64	<.001	0.02
Model 2	0.19	3.20	.001	0.01
Memory test score part 1				
Unadjusted	0.49	3.94	<.001	0.03
Model 1	0.40	3.08	.002	0.02
Model 2	0.39	3.05	.002	0.02
Memory test score part 2				
Unadjusted	0.39	3.36	.001	0.02
Model 1	0.31	2.52	.01	0.01
Model 2	0.27	2.20	.03	0.01

Model 1 includes sex, socio-economic status, educational level and age; Model 2 additionally includes BMI, alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication, stress task commitment and baseline SBP.

Table 5.4. Regression models AH-4 and memory test and DBP reactivity.

	β	t	p	R ² change
AH-4 correct items				
Unadjusted	0.08	3.54	<.001	0.02
Model 1	0.09	3.32	.001	0.02
Model 2	0.08	3.11	.002	0.01
Memory test score part 1				
Unadjusted	0.19	3.64	<.001	0.02
Model 1	0.18	3.26	.001	0.02
Model 2	0.17	3.07	.002	0.02
Memory test score part 2				
Unadjusted	0.13	2.55	.01	0.01
Model 1	0.12	2.19	.03	0.01
Model 2	0.11	2.00	.05	0.01
Model 1 includes sex, socio-economic status, educational level and age; Model 2 additionally includes BMI, alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication, stress task commitment and baseline DBP				

Table 5.5. Regression models AH-4 and memory test and HR reactivity.

	β	t	p	R ² change
AH-4 correct items				
Unadjusted	0.10	4.08	<.001	0.02
Model 1	0.07	2.64	.01	0.01
Model 2	0.06	2.24	.03	0.01
Memory test score part 1				
Unadjusted	0.19	3.43	.001	0.02
Model 1	0.14	2.47	.01	0.01
Model 2	0.14	2.50	.01	0.01
Memory test score part 2				
Unadjusted	0.21	3.97	<.001	0.02
Model 1	0.17	3.02	.003	0.01
Model 2	0.15	2.79	.01	0.01
Model 1 includes sex, socio-economic status, educational level and age; Model 2 additionally includes BMI, alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication, stress task commitment and baseline HR.				

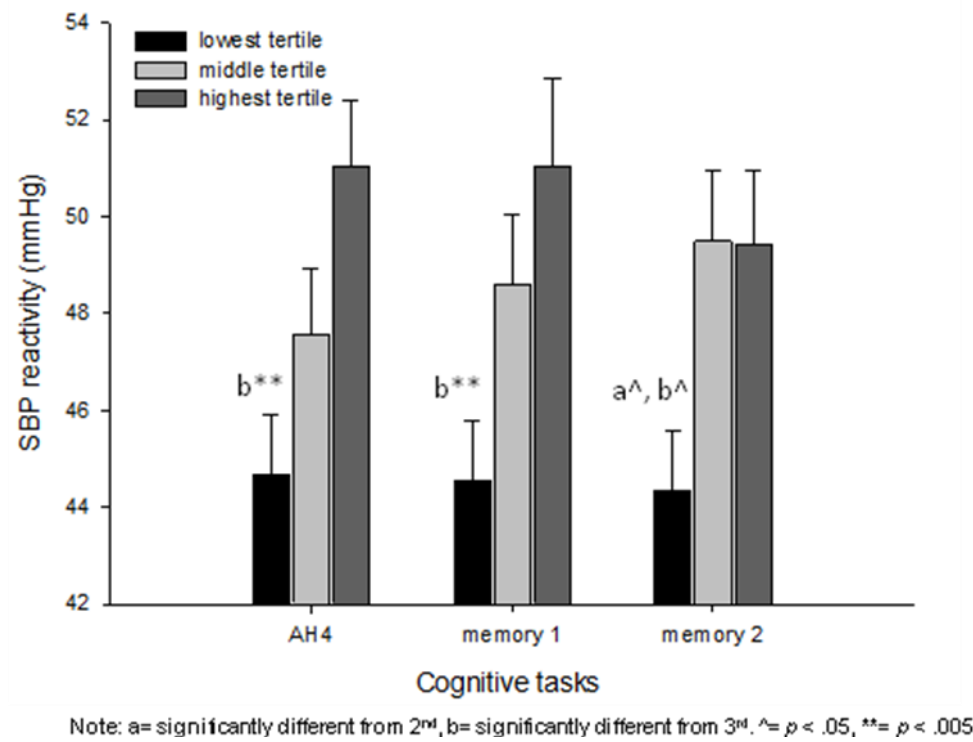


Figure 5.1. Mean (SD) SBP reactivity for tertiles of cognitive ability scores

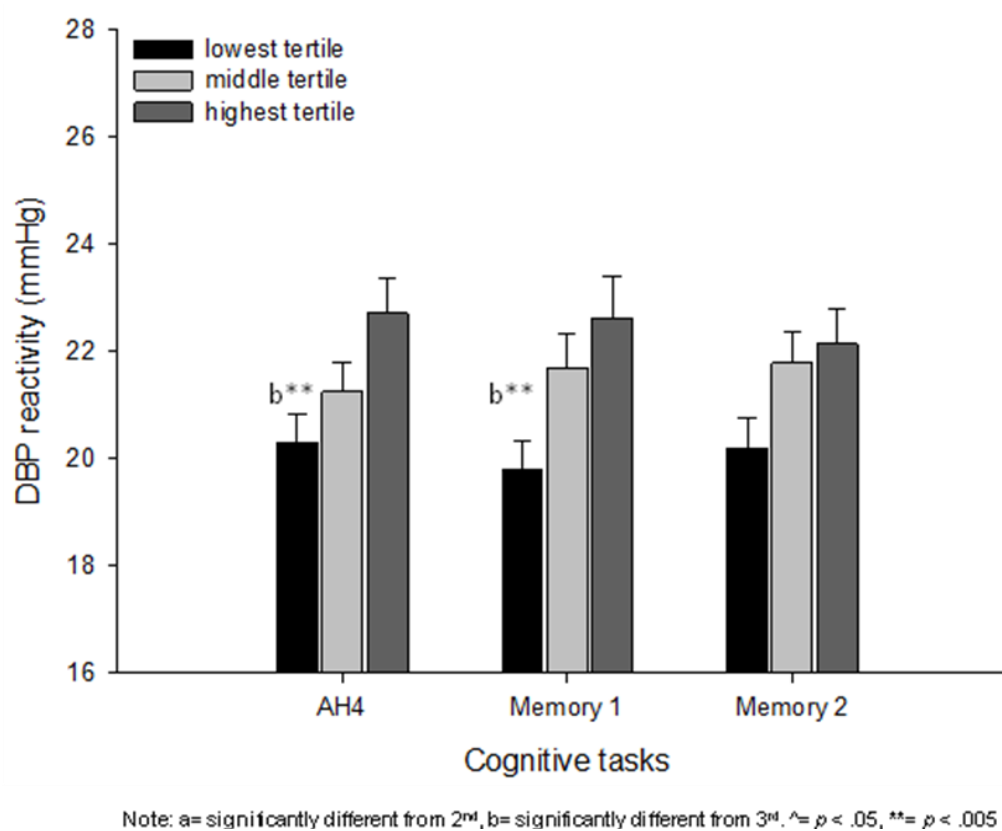


Figure 5.2. Mean (SD) DBP reactivity for tertiles of cognitive ability scores

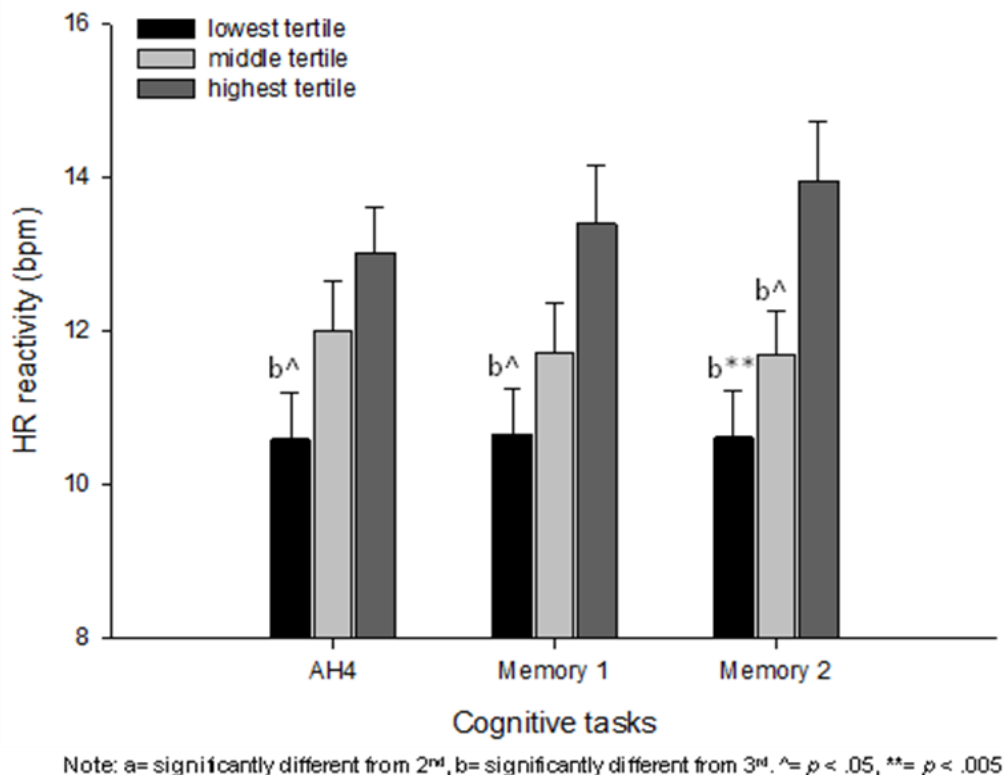
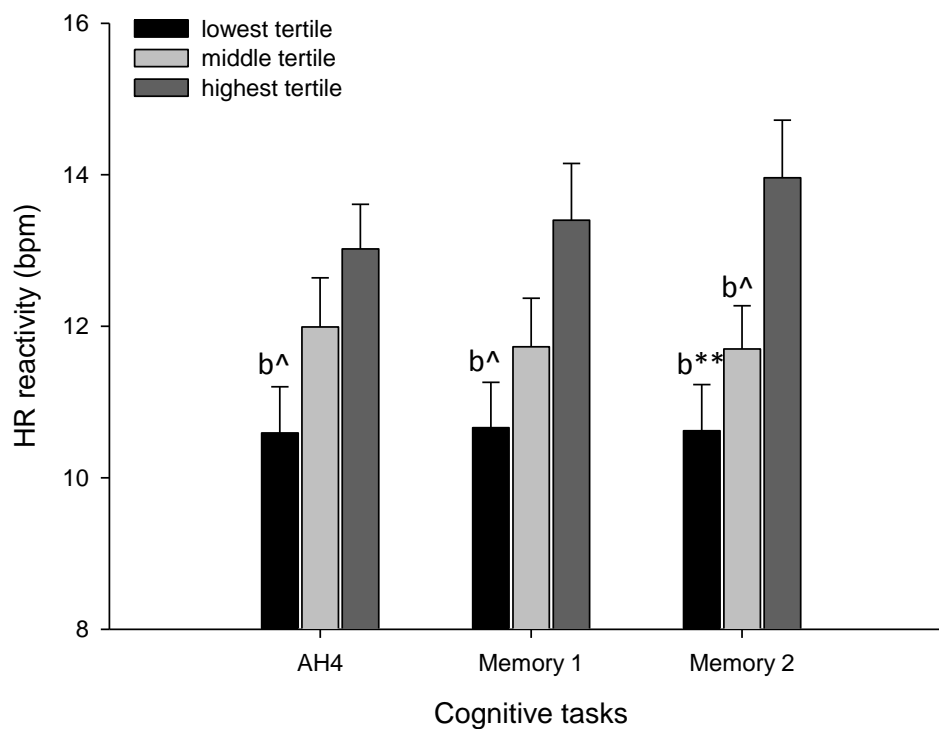


Figure 5.3. Mean (SD) HR reactivity for tertiles of cognitive ability scores

We also analysed the cardiovascular reactivity data as mean cardiovascular reactivity (mean activity across the three tasks - baseline). The outcomes were almost identical to those reported from the peak response analyses above, with one exception: the previously significant association between memory 2 performance and SBP reactivity was no longer statistically significant ($p = .06$, whereas previously it was $p = .05$).

In the models adjusting only for baseline cortisol, all three of the cognitive ability tasks were positively associated with cortisol AUC: the flatter the AUC the lower the cognitive ability. These associations are illustrated by plotting tertiles of cognitive ability scores against AUC in Figure 5.4. For this illustration, actual arithmetic mean (*SE*) cortisol AUC values were used. For memory 1 and memory 2 tasks, the associations between cognitive ability and cortisol AUC remained statistically significant in the two models adjusting for additional covariates. However, in the case of AH-4, additional adjustment attenuated the associations to nonsignificance. The summary statistics for the regression models are presented in Table 5.6.



Note: a= significantly different from 2nd, b= significantly different from 3rd. ^ = $p < .05$, ** = $p < .005$

Figure 5.4. Mean (SD) AUC cortisol for tertiles of cognitive ability scores

Table 5.6. Regression models AH-4 and memory test and AUC for cortisol.

	β	t	p	R ² change
AH-4 correct items				
Model 1	0.003	2.46	.01	0.01
Model 2	0.001	0.74	.46	.000
Model 3	0.000	0.13	.90	0.00
Memory test score part 1				
Model 1	0.011	3.53	< .001	0.02
Model 2	0.010	3.19	.002	0.01
Model 3	0.009	2.83	.005	0.01
Memory test score part 2				
Model 1	0.011	3.66	< .001	0.02
Model 2	0.009	3.05	.002	0.01
Model 3	0.008	2.56	.01	0.01

Model 1 adjusts only for baseline cortisol; Model 2 additionally includes sex, socio-economic status, educational level and age; Model 3 additionally includes alcohol consumption, smoking, use of anti-hypertensive medication, use of anti-depressant or anxiolytic medication and stress task commitment; β in percent difference based on log-transformed AUC for cortisol.

Discussion

This study examined the cross-sectional association between cardiovascular and cortisol stress reactivity and cognitive ability, as indexed by scores on the AH-4 test of verbal and numerical reasoning and by two memory tasks: immediate and delayed recall. Low SBP, DBP, and HR reactions to acute stress were associated with low AH-4 test scores and poorer performance on the two memory tasks. *Post hoc* analyses of tertiles of AH-4 and memory task scores indicated a positive dose-response relationship between cognitive ability and cardiovascular reactivity. These associations between cardiovascular reactivity and cognitive ability remained statistically significant in regression models that adjusted for age, sex, socioeconomic status, educational level, BMI, alcohol consumption, smoking, use of antihypertensive medication, use of antidepressant or anxiolytic medication, stress task commitment, and baseline cardiovascular activity. The fact that the positive associations between cardiovascular reactivity and cognitive ability, with one exception, survived adjustment for stress task commitment suggests that present results cannot be accounted for by participants of low cognitive ability disengaging from the stress challenges. Low cortisol AUC was also associated with poorer AH-4 scores and memory performance. These associations survived adjustment for additional covariates in the case of memory performance but not in the case of AH-4 scores. *Post hoc* analyses using tertiles of cognitive ability suggest a dose response relationship between memory performance and cortisol stress reactivity as indexed by AUC.

It is noteworthy that there were no significant associations between cognitive ability and baseline cardiovascular levels, given the extant literature indicating a relationship between resting blood pressure and cognitive function (Elias, Elias, Robbins, & Budge, 2004; Robbins, Elias, Elias, & Budge, 2005; Waldstein, 1994; Waldstein, Giggey, Thayer, & Zonderman, 2005). However, cognitive deficits may be manifest mainly in those with

hypertensive or borderline hypertensive blood pressure levels (Novak & Hajjar, 2010). In addition, both cross-sectional and longitudinal relationships to blood pressure have been found to be predominately nonlinear and moderated by a range of factors including age, education, and antihypertensive medication (Waldstein et al., 2005). With one exception, there was also no association between cognitive ability and baseline cortisol.

The direction of the relationship between cognitive ability and cardiovascular reactivity is in line with that observed in two earlier studies, which found that lower cardiovascular reactivity was associated with poorer performance on the mental stress task (DeGangi et al., 1991; Duschek et al., 2009). However, it should be conceded that two other studies failed to find an association between reactivity and cognitive ability as revealed by performance on the stress task (Bucks & Seljos, 1994; Wright et al., 2005). Only one other published study in the context has assessed cognitive ability independently of stress task performance; a recent analysis of a substantial cohort from the West of Scotland 20-07 found a positive retrospective association between AH-4 scores and cardiac reactions to a mental arithmetic stress 7 years later (Ginty et al., 2011). The present analyses indicate that the positive relationship between cognitive ability and reactivity may extend to blood pressure, as well as cardiac reactivity. That the relationship holds for memory task performance as well as AH-4 scores indicates the generality of the association between blunted cardiovascular reactivity and poor cognitive ability.

The present finding of a positive association between cognitive ability, particularly memory performance, and cortisol stress reactivity is in line with the results of three previous studies showing that low cortisol reactivity was associated with poorer performance on a variety of cognitive tasks (al'Absi et al., 2002; Blair et al., 2005; Domes et al., 2002). In addition, there has also been an observation from a small-scale study of

elderly individuals that cortisol reactivity was lower in those with poorer declarative memory before and after the stressful exposure (Lupien et al., 1997). However, it should be conceded that other studies report a negative association between cognitive ability and cortisol reactivity, although for men, but not for women (Wolf et al., 2001), and in two instances for cognitive tasks that also served as the stress exposure (al'Absi et al., 2002; Wright et al., 2005). In the present study, multivariate analyses abolished the positive association between AH-4 scores and cortisol AUC. It is possible that this reflected a reduction in power in the cortisol analyses as a function of missing data. However, our analyses included substantially more participants than previous studies of cortisol reactivity and cognitive ability. Accordingly, it is also possible that robust positive associations between cognitive ability and cortisol reactivity are found mainly for tasks that involve memory and recall. It is perhaps worth noting in this context that two of the four studies above reporting an association between low cortisol reactivity and poorer cognitive ability used a memory task to measure cognition (Domes et al., 2002; Lupien et al., 1997).

The present findings are also consistent with a growing body of cross-sectional and prospective evidence that low, not high, cardiovascular and/or cortisol reactivity are associated with a range of adverse health and behavioural outcomes, such as obesity (Carroll et al., 2008; Phillips, 2011), symptoms of depression (Carroll, Phillips, Hunt, & Der, 2007; De Rooij, Schene, Phillips, & Roseboom, 2010; Phillips et al., 2011; Rottenberg, Clift, Bolden, Salomon, 2007; Salomon, Clift, Karlsdottir, & Rottenberg, 2009; York et al., 2007), and bulimia (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012; Koo-Loeb, Pedersen, & Girdler, 1998). Low reactivity has also been associated with tobacco and alcohol dependence, as well as risk of dependence (al'Absi, 2006; al'Absi, Hatuskami, & Davis, 2005; Girdler, Jammer, Jarvik, Soles, &

Shapiro, 1997; Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002; Phillips, Der, Hunt, & Carroll, 2009; Roy, Steptoe, & Kirschbaum, 1994), and exercise dependence (Heaney, Ginty, Carroll, & Phillips, 2011).

Further, our results are consistent with the recent contention that relatively low cardiovascular reactions to acute stress may be a peripheral marker of central motivational dysregulation (Carroll, Lovallo, & Phillips, 2009; Carroll, Phillips, & Lovallo, 2011; Lovallo, 2011). By central motivational dysregulation, we mean the suboptimal functioning of those systems in the brain, converging at the striatum and ventromedial prefrontal cortex, which appear to shape the motivation of our behaviour. These may be precisely the same circuits that support physiological reactivity (Carroll et al., 2009; Carroll et al., 2011; Lovallo, 2011). As cognitive performance requires the integrity of such motivational systems (Busato, Prins, Elshout, & Hamaker, 2000; Dweck, 1986; McClelland, Atkinson, Clark, & Lowell, 1953; Pintrich & Schunk, 1986), it would be expected that lower rather than higher cardiovascular reactivity would be associated with poorer subsequent cognitive ability, which is precisely what was observed in the current study.

The present study is not without limitations. First, it should be acknowledged that the observed effect sizes are small. However, our effects for cardiovascular reactivity are of the same order as the positive associations between cardiovascular reactivity and future resting blood pressure in other studies (Carroll et al., 1995, 2001, 2003; Markovitz et al., 1998; Matthews et al., 1993; Newman et al., 1999). Second, only blood pressure and HR reactivity were measured. It could have proved instructive to have a more comprehensive assessment of hemodynamics, such as that afforded by impedance

cardiography. Cardiovascular reactivity would appear to reflect both β -adrenergic and parasympathetic influences (Balanos et al., 2010; Sloan, Korten, & Myers, 1991). Thus, low cardiovascular reactivity could reflect reduced β -adrenergic drive or less withdrawal of vagal tone during the stress task. Regrettably, in the present study we cannot determine which of these was the predominant mechanism for low cardiac reactivity. Third, determining causality and the direction of causality in cross-sectional studies is impossible. Further, confounding by unmeasured variables can never be wholly discounted. However, we did adjust for a broad range of potential confounders, indeed more than any previous study. Fourth, at the time of testing no Dutch version of the AH-4 was available, so it was translated internally (De Rooij, Wouters, Yonker, Painter, & Roseboom, 2010). Also, it was not possible to separate the verbal and numeric scores of the total AH-4 score. A separation of these subscales may have shown reactivity to stressors to be associated with one subscore more than with the other. However, a previous study has shown reactivity to be associated with both subscales (Ginty et al., 2011). Fifth, although we would argue that the separation of stress exposure from cognitive ability assessment in the present study should be regarded as a strength, it is also possible that the time-limited AH-4 task itself acted as a stressor and elicited individual differences in reactivity that may have correlated with those observed during the designated stress tasks. However, since stress reactivity was not measured during the AH-4, we have no way of determining whether this was the case. Sixth, this is a unique population, and it has been suggested that early life adversity may predispose individuals to lifelong vulnerability to stress. However, a previous study using this population showed individuals who experienced prenatal exposure to the Dutch famine did not differ in cortisol stress reactivity from those who did not (De Rooij et al., 2006). Finally, it was not possible to derive performance scores for the stress tasks

used in this study. Nevertheless, we do have a measure of commitment to the task and have included this as a covariate in the fully adjusted analyses.

In conclusion, we observed a robust cross-sectional positive association between cardiovascular and cortisol reactivity and cognitive ability assessed independently of mental stress task performance. Our results are consistent with the notion that low or blunted cardiovascular and cortisol stress reactivity may be associated with a range of adverse behavioural and health outcomes, and low reactivity

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Chapter 6

Heart Rate Reactivity is Associated with Future Cognitive Ability and Cognitive Change in a Large Community Sample

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Abstract

The relationship between cardiovascular reactions to acute mental challenge in the laboratory and cognitive ability has received scant attention. The present study examined the association between reactivity and future cognitive ability. Heart rate and blood pressure reactions to a mental stress task were measured in 1647 participants comprising three distinct age cohorts. Cognitive ability was assessed using the Alice Heim-4 test of general intelligence and choice reaction time 5 and 12 years later. High heart rate reactivity was related to higher general intelligence scores and faster choice reaction times at both follow-ups. High heart rate reactivity was also associated with a smaller decline in cognitive ability between assessments. These associations were still evident following adjustment for a wide range of potentially confounding variables. The present results are consistent with the notion that high reactivity may not always be a maladaptive response and that low or blunted reactivity may also have negative corollaries.

Keywords: Blood pressure, Cognitive ability, Cognitive change, Heart rate, Reactivity

Little is known about the association between cardiovascular stress reactivity and cognitive function. In a study of infants, greater suppression of a heart period based index of vagal tone during the cognitive challenge afforded by the Bayley Scale of Infant Development was associated with more mature cognitive skills and more coordinated motor behaviour (DeGangi, DiPietro, Greenspan, & Porges, 1991). A broadly similar outcome emerged from a more recent study of cardiovascular reactions to a task in which young adults were required to identify a target stimulus among a variety of distractor items (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009): R-wave to pulse interval, an index of sympathetic activity, was negatively associated with task performance, whereas respiratory sinus arrhythmia, an index of vagal tone, was positively related to performance. The authors interpret these outcomes as suggesting an association between enhanced sympathetic and reduced vagal cardiovascular influences and improved cognitive-attentional functioning. In contrast, no association between cardiovascular reactivity to memory tasks and task performance has been reported in studies of young (Bucks & Seljos, 1994) and older adults (Wright, Kunz-Ebrecht, Iliffe, Foese, & Steptoe, 2005), although in the latter study, superior memory performance was associated with faster heart rate recovery following task exposure. Given the variations in study samples, the physiological parameters measured, and the cognitive tasks employed, it is not surprising that no clear consensus emerges from these studies. With one exception (Wright et al., 2005), all of the studies were small scale and did not adjust for potential confounding variables. More importantly, all of these previous studies measured cognitive ability as performance on the stress reactivity challenge. Stronger tests of the association between cognitive ability and cardiovascular reactivity to mental stress would be afforded by using measures of cognitive ability that are independent of the mental stress task employed to elicit reactivity.

In the present study, cardiovascular reactions to acute stress were assessed in a substantial community sample and cognitive ability was then measured 5 and 12 years later using a standard measure of general intelligence and choice reaction time. Thus, cognitive ability was measured independently of and at different times from mental stress task exposure. We have recently reported from analyses restricted to the oldest of three age cohorts in the West of Scotland study, retrospective associations between reactivity and cognitive ability measured 7 years earlier; low heart rate reactivity was characteristic of those with relatively low prior cognitive ability (Ginty, Phillips, Der, Deary, & Carroll, 2011). The present analyses are prospective with respect to cognition and data were available for all three age cohorts. Thus, in our previous study we established the possibility of a causal pathway from low cognitive ability to blunted heart rate reactivity. In the present analyses, we test the additional possibility that reactivity predicts cognitive ability in the future, as well as any change in cognitive performance between the two follow-ups. It is also worth noting that choice reaction time has been found to correlate negatively with more traditional measures of general intelligence and indeed has been regarded as a measure of cognitive ability (Rabbitt & Goward, 1994). Based on the balance of previous evidence, including our own recent finding of a retrospective positive association between heart rate reactivity and cognitive ability, as well as research testifying to an association between low or blunted reactivity and a number of adverse health and behavioural outcomes (Carroll, Lovallo, & Phillips, 2009a; Carroll, Phillips, & Lovallo, 2011; Phillips, 2011), it was hypothesised that lower heart rate reactivity would be associated prospectively with relatively lower cognitive ability and slower choice reaction times. Thus, what we are hypothesising is that there might be a bi-directional relationship between cognitive ability and reactivity.

Method

Participants

Data were collected as part of the West of Scotland Twenty-07 Study. Participants were from Glasgow and surrounding areas in Scotland, and have been followed up at regular intervals since the baseline survey in 1987 (Ford, Ecob, Hunt, Macintyre, & West 1994). The study's principal aim was to investigate the processes that generate and maintain sociodemographic differences in health (Macintyre, 1987). Participants were chosen randomly with probability proportional to the overall population of the same age within a post code area (Ecob, 1987). Thus, this is a clustered random stratified sample. Three narrow age cohorts were chosen (aged 15, 35, and 55 years at entry). More complete details of the study are available elsewhere (Carroll, Phillips, & Der, 2008; Ford et al., 1994; Phillips, Der, & Carroll, 2009a, Phillips, Der, Hunt, & Carroll, 2009b).

The data reported here are from the third, fourth, and fifth followups. The mean (SD) temporal lag between the third and fourth followup visits was 5.5 (1.00) years and between the third and fifth followup visits was 12.4 (0.40) years. Cardiovascular stress reactivity was assessed for 1647 participants at the third follow-up. The sample at this time point comprised 592 (36%) 24-year-olds, 624 (38%) 44-year olds, and 431 (26%) 63-year-olds. There were 890 (54%) women and 757 (46%) men, and 772 (47%) were from manual and 870 (53%) from non-manual occupation households. Household occupational status was unavailable for five participants. Overall mean (SD) age at the third follow-up visit was 42.2 (15.44) years. The mean (SD) ages of the young, middle-aged, and older age cohorts were 24.20 (0.45), 44.56 (0.84), and 63.57 (0.61) years. Cognitive ability, using the Alice Heim-4 (AH-4) test and choice reaction time (CRT), was assessed at the fourth and fifth follow-ups. The attrition rate, largely as a result of relocation, between the third and fourth follow-ups was 23%; CRT data were available for 1251 participants at the fourth follow-up. There was little attrition (5%) between the fourth and fifth follow-up and reaction time

data were available for 1189 participants at the fifth follow-up. AH-4 scores were available for 1170 and 1148 participants at the fourth and fifth follow-ups respectively. This study was approved by the appropriate Ethics Committees.

Apparatus and Procedure

Participants were interviewed and tested in a quiet room in their homes by trained nurses. During the third follow-up visit household occupational group was classified as manual or non-manual from the occupation of the head of household, using the Registrar General's Classification of Occupations (1980). Head of household was usually the man. Long-standing illness or disability status, hereafter referred to by the latter term, was determined by response to the question, 'Do you have any long-standing illness, disability, or infirmity? By longstanding I mean anything that has troubled you over a period of time or that is likely to affect you over a period of time?' Height and weight were measured and body mass index (BMI) computed. Symptoms of depression were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The HADS is a well-recognised assessment instrument that comprises 14 items, 7 measuring depression and 7 measuring anxiety. The depression subscale emphasises anhedonia and largely excludes somatic items.

Participants then undertook an acute psychological stress task, the paced auditory serial addition test (PASAT), which has been shown in numerous studies reliably to perturb the cardiovascular system (Ring, Burns, & Carroll, 2002; Winzer et al., 1999) and to demonstrate good temporal stability of reactivity (Willemsen et al., 1998). The task comprised a series of single digit numbers presented by audiotape and participants were requested to add sequential number pairs, and at the same time retain the second of the pair in memory for addition to the next number presented, and so on throughout the series.

Answers were given orally and, if the participants faltered, they were instructed to recommence with the next number pair. The first sequence of 30 numbers was presented at a rate of one every 4 s, and the second sequence of 30 numbers was presented at a rate of one every 2 s. The whole task took 3 min, 2 min for the slower sequence, and 1 min for the faster sequence. A brief practice was given to ensure that participants understood the requirements of the task.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) values were determined by a semiautomatic sphygmomanometer (model 705CP, Omron, Weymouth, UK), a device recommended by the European Society of Hypertension (O'Brien, Waeber, Parati, Staessen, & Myers, 2001). After the interview (at least an hour), there was a formal 5-minute period of relaxed sitting, at the end of which a resting baseline reading of SBP, DBP, and HR was taken. PASAT instructions were then given, followed by a brief practice. Two SBP, DBP, and HR readings were taken during the PASAT, the first initiated 20 s into the task (during the slower sequence of numbers), and the second initiated 110 s later (at the same point during the faster sequence). For all readings, the nurses ensured that the participant's elbow and forearm rested comfortably on a table at heart level. The two task readings were averaged and the resting baseline value was subsequently subtracted from the resultant average task value to yield reactivity measures for SBP, DBP, and HR for each participant.

At both the fourth and fifth follow-up visits, the Alice Heim-4 (AH-4) test, a measure of general mental ability (Deary, Der, & Ford, 2001), was administered; administration and scoring were carried out as described in the test manual (Heim, 1970). The test consisted of 12 practice questions followed by 33 items measuring numerical reasoning ability and 32 items measuring verbal reasoning ability. The test has been used in other population

studies of individuals in the same age range (Singh-Manoux, Ferrie, Lynch, & Marmot, 2005; Rabbitt, Diggle, Smith, Holland, & McInnes, 2001).

At the fourth and fifth follow-ups, participants undertook a CRT task using a portable device originally designed for the UK Health and Lifestyle Survey (Cox et al., 1987). The device consisted of five keys arranged in a shallow arc; the keys were numbered 1, 2, 0, 3, and 4. Participants were asked to rest the 2nd and 3rd finger of each hand on the keys labelled 1, 2, 3, and 4 and press the corresponding key when one of the four digits appeared above. Participants were given eight practice trials and 40 test trials; the digits 1–4 appeared 10 times during the 40 trials in a random order. The amount of practice given to participants is similar to most studies that relate reaction times to intelligence differences (Deary, 2000). CRT was measured in milliseconds.

Statistical analysis

Differences in AH-4 scores and CRTs between sexes, household occupational group, and age cohort were explored using analysis of variance (ANOVA). Repeated-measures ANOVAs, using baseline and task values, were undertaken to confirm that the PASAT perturbed cardiovascular activity. Partial eta squared (η^2) is used as a measure of effect size. The relationship between AH-4 scores and CRTs were investigated by Pearson's correlation. Linear regression analyses were used to determine whether cardiovascular reactivity was associated with AH-4 score and CRT 5 and 12 years later. A series of hierarchical linear regressions were undertaken to determine whether any effects that emerged from the primary analyses withstood adjustment for potential confounding variables. The possible confounders selected were age cohort, sex, household occupational group, disability status, HADS depression, BMI, and baseline cardiovascular levels. All of these have been related to reactivity and/or cognitive ability in this cohort (Carroll et al.,

2000, Carroll, Phillips, Hunt, & Der, 2007, Carroll et al., 2008; Phillips et al., 2011). The main regression analyses were repeated separately for numerical reasoning and verbal reasoning at the two time points testing both unadjusted and fully adjusted models. Finally, regression models were tested that examined the change in cognitive ability over time. In these, AH-4 score and CRT at the fifth follow-up were the dependent variables, cardiovascular reactivity was the independent variable, and we adjusted for earlier AH-4 score and CRT at the fourth follow-up in each case. Again, we also tested models that additionally adjusted for all the other covariates.

Results

Socio-demographics and cognitive ability

The overall mean (SD) AH-4 scores and mean (SD) CRTs at the fourth and fifth follow-ups were 35.28 (11.41) and 35.34 (11.31) respectively and 619.8 (153.31), and 629.5 (153.31) milliseconds respectively. The non-manual household group registered higher AH-4 scores than the manual occupational group at both follow-ups, $F(1,1164) = 189.25$, $p < .001$, $\eta^2 = .140$, $F(1, 1143) = 115.65$, $p < .001$, $\eta^2 = .092$, respectively, as well as faster CRTs, $F(1, 1245) = 39.26$, $p < .001$, $\eta^2 = .031$, $F(1, 1184) = 15.60$, $p < .001$, $\eta^2 = .013$, respectively. Males displayed significantly higher AH-4 scores at the fourth follow-up than females, $F(1,1169) = 3.95$, $p = .05$, $\eta^2 = .003$; there were no significant difference between genders at the fifth follow-up, nor for CRT at either follow up. The younger cohort registered higher AH-4 scores and faster CRTs than the middle cohort who, in turn, registered higher AH-4 scores and shorter CRTs than the oldest cohort at the fourth follow-up, $F(2,1169) = 73.96$, $p < .001$, $\eta^2 = .112$, and $F(2,1249) = 398.47$, $p < .001$, $\eta^2 = .390$, respectively, and fifth follow-up, $F(2, 1147) = 122.71$, $p < .001$, $\eta^2 = .177$, and $F(2, 1187) = 354.64$, $p < .001$, $\eta^2 = .370$, respectively. Individuals who reported long-standing illness or disability scored substantially lower on the AH4, $F(1,1169) = 22.43$, $p < .001$, η^2

= .019, and $F(1,1147) = 28.80, p < .001, \eta^2 = .025$, and had markedly slower CRTs, $F(1, 1249) = 45.86, p < .001, \eta^2 = .035$, $F(1, 1187) = 41.40, p < .001, \eta^2 = .034$, at the fourth and fifth follow-ups, respectively. The summary statistics are reported in Table 6.1. AH-4 scores at the two follow-ups were positively correlated, $r(1146) = .87, p < .001$, as were CRTs, $r(1030) = .70, p < .001$. AH4 scores correlated negatively with CRT at both the fourth, $r(1123) = -.53, p < .001$, and fifth, $r(1136) = -.55, p < .001$, follow-ups.

Cardiovascular reactions to acute stress

Two-way (baseline x task) repeated measures ANOVA indicated that on average the PASAT significantly increased cardiovascular activity: for SBP, $F(1,1646) = 1562.32, p < .001, \eta^2 = .487$, for DBP, $F(1,1646) = 1066.62, p < .001, \eta^2 = .393$; and for HR, $F(1,1646) = 1132.96, p < .001, \eta^2 = .408$. The mean baseline and reactivity values are presented in Table 6.2.

HR reactivity declined with age, $F(2, 1644) = 21.11, p < .001, \eta^2 = .408$; with the youngest cohort exhibiting higher reactivity than the middle cohort who, in turn showed higher reactivity than the eldest cohort ($p < .05$ in each case). HR reactivity was also greater in men, $F(1,1645) = 5.23, p = .02, \eta^2 = .003$, and in participants from non-manual occupational group households, $F(1,1640) = 21.08, p < .001, \eta^2 = .013$. SBP reactivity varied significantly among the age cohorts, $F(2,1644) = 6.81, p < .001, \eta^2 = .008$, with the youngest cohort having significantly lower reactivity than the other two cohorts ($p < .05$ in both cases). Women had smaller SBP reactions than men, $F(1,1645) = 16.61, p < .001, \eta^2 = .010$. DBP reactivity did not vary significantly with age cohort, sex, or household occupational group. The statistics reported above relate to significant group by baseline/task condition interactions. However, for the sake of illustration we report baseline and reactivity in Table 6.2.

Table 6.1. Mean (SD) AH-4 scores and CRT by age cohort, sex, occupational group and disability status at the fourth and fifth follow-ups

	AH-4 scores					CRT				
	N		Mean (SD)			N		Mean (SD)		
	4th	5th	4th	5th		4th	5th	4th	5th	
Age cohort										
Youngest	396	429	38.9 (9.70)	39.8 (9.73)		429	433	538.7 (72.51)	535.0 (63.18)	
Middle	478	485	36.2 (11.27)	35.6 (10.84)		496	501	621.1 (86.6)	629.3 (94.9)	
Eldest	326	234	29.0 (10.92)	26.7 (10.04)		326	255	724.5 (111.5)	790.2 (210.40)	
Sex										
Male	529	530	36.0 (11.37)	35.7 (11.11)		574	541	616.2 (110.49)	626.0 (163.58)	
Female	641	618	34.7 (11.41)	35.0 (11.48)		677	648	622.8 (118.00)	632.4 (143.97)	
Occupational group										
Manual	507	495	30.4 (11.10)	31.44 (10.95)		562	525	642.0 (124.20)	648.9 (178.22)	
Non-manual	658	649	39.1 (10.17)	38.4 (10.63)		684	660	601.7 (102.93)	613.8 (128.21)	
Disability status										
No disability status	1136	1119	35.6 (11.32)	35.6 (11.22)		1212	1156	615.9 (110.77)	624.7 (148.68)	
Disability	34	29	26.2 (10.63)	24.3 (9.43)		396	396	740.0 (160.62)	796.0 (213.54)	

Table 6.2. Mean (SD) values of SBP, DBP, and HR baseline and reactivity by age cohort, sex, and occupational status

	SBP		DBP		HR	
	Baseline	Reactivity	Baseline	Reactivity	Baseline	Reactivity
Age cohort						
Youngest (n = 592)	120.0 (15.07)	10.1 (10.24)	73.4 (10.08)	6.8 (9.04)	67.5 (11.00)	10.0 (10.56)
Middle (n = 624)	127.1 (18.08)	12.3 (11.44)	80.6 (11.13)	7.1 (8.03)	66.7 (11.17)	7.7 (10.00)
Eldest (n = 431)	144.4 (21.68)	12.3 (13.92)	83.8 (11.17)	7.0 (8.92)	65.7 (9.92)	6.1 (7.74)
Sex						
Male (n = 757)	134.7 (18.25)	12.8 (11.77)	81.2 (11.18)	7.2 (8.43)	64.7 (10.43)	8.7 (9.73)
Female (n = 890)	124.3 (21.07)	10.4 (11.70)	76.8 (11.56)	6.8 (8.81)	68.4 (10.84)	7.6 (9.83)
Occupational group						
Manual (n = 722)	130.5 (21.44)	11.1 (12.22)	79.3 (11.93)	6.5 (9.07)	67.0 (11.26)	6.9 (9.53)
Non-manual (n = 872)	127.8 (19.58)	11.8 (11.39)	78.4 (11.29)	7.3 (8.24)	66.5 (10.40)	9.1 (9.90)

Justification for separate regression analyses for the five and 12 year follow-ups

In order to justify the separate analyses for the two follow-ups, we tested the time x HR reactivity interaction in a fully adjusted linear mixed model. The interaction was significant for both AH-4 scores, $t(914) = 2.06, p = .04$, and CRT, $t(1005) = 2.40, p = .02$.

Cardiovascular reactivity and future AH-4 performance scores and CRT five years later

In the first model, with no adjustment, HR reactivity was associated with future AH-4 performance scores, $\beta = .200, p < .001, \Delta R^2 = .040$; individuals with lower HR reactivity

had poorer AH-4 scores five years later. SBP ($p = .33$) and DBP ($p = .95$) reactivity did not significantly predict future AH-4 scores. In regression analyses that adjusted for age cohort, sex, household occupational group, disability status, HADS depression, BMI, and baseline cardiovascular levels, HR reactivity continued to be associated with AH-4 scores, $\beta = .107$, $p = <.001$, $\Delta R^2 = .010$, with the association in the same direction. The final regression is shown in Table 6.3. SBP and DBP reactivity did not predict cognitive ability at the fourth follow-up in this fully adjusted model, $p = .25$ and $.67$, respectively. The unadjusted association with HR reactivity are illustrated by plotting AH-4 scores against tertiles of reactivity (Figure 6.1a). AH-4 scores varied significantly with tertiles of HR reactivity, $F(2,1167) = 27.27$, $p < .001$, $\eta^2 = .045$. The relationship between SBP and DBP and AH-4 scores were again non-significant. In the unadjusted model, HR reactivity was negatively associated with CRT at the fourth follow-up, $\beta = -.194$, $p < .001$, $\Delta R^2 = .038$. SBP ($p = .35$) and DBP ($p = .89$) did not significantly associated with future choice reaction time; individuals with lower HR reactivity had longer CRTs five years later. In the model that adjusted for age cohort, sex, household occupational group, disability status, HADS depression, BMI, and baseline cardiovascular levels, HR reactivity was still negatively associated with CRT, $\beta = -.056$, $p = .018$, $\Delta R^2 = .003$. The final regression is shown in Table 6.4. SBP reactivity was also negatively associated with CRT in this fully adjusted model, $\beta = -.055$, $p = .016$, $\Delta R^2 = .003$. DBP reactivity was not associated with future choice reaction time ($p = .78$). The unadjusted association between HR reactivity and CRT are illustrated by plotting CRT scores against tertiles of reactivity (Figure 6.2a). CRT varied among the tertiles of HR reactivity, $F(2,1284) = 27.63$, $p < .001$, $\eta^2 = .042$.

Table 6.3. Predictors of AH-4 score at the fourth and fifth follow-up in the fully adjusted heart rate reactivity regression model

	AH-4 scores 4 th follow-up			AH-4 scores 5 th follow-up		
	β	p	ΔR^2	β	p	ΔR^2
Age cohort	-.263	<.001		-.361	<.001	
Sex	-.051	.050		-.031	.226	
Occupational group	-.352	<.001		-.282	<.001	
Disability status	-.061	.019		-.084	.001	
HADS Depression	-.083	.001		-.122	<.001	
BMI	-.021	.438		-.006	.804	
Baseline heart rate	-.006	.814	.254	.013	.621	.284
Heart rate reactivity	.107	<.001	.010	.130	<.001	.015

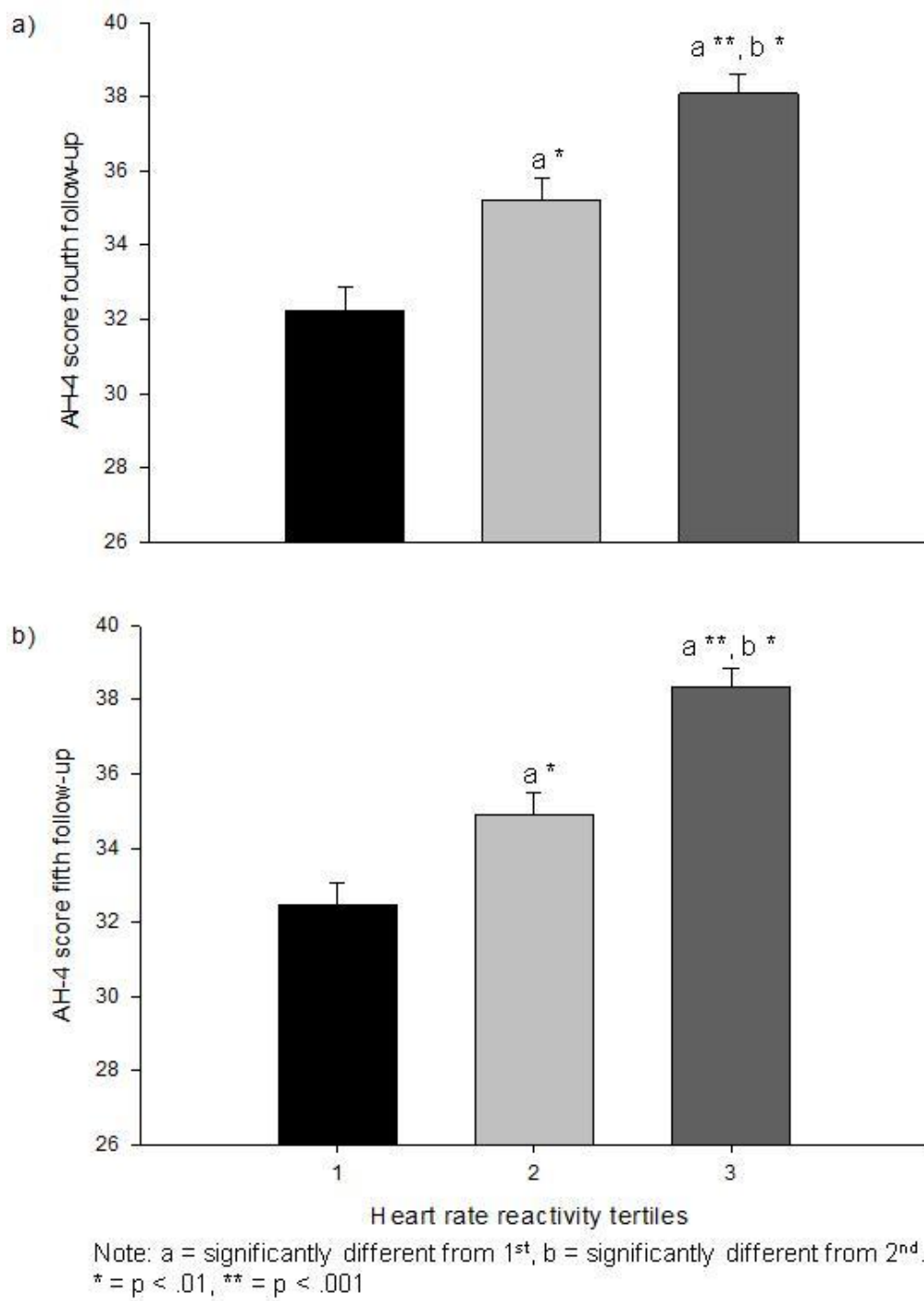


Figure 6.1. a) AH-4 scores at the fourth follow-up by tertiles of heart rate reactivity, b) AH-4 scores at the fifth follow-up by tertiles of heart rate reactivity

Table 6.4. Predictors of CRT at the fourth and fifth follow-up in the fully adjusted heart rate reactivity regression model

	AH-4 scores 4 th follow-up			AH-4 scores 5 th follow-up		
	β	p	ΔR^2	β	p	ΔR^2
Age cohort	.584	<.001		.561	<.001	
Sex	.021	.336		.026	.271	
Occupational group	.124	<.001		.084	<.001	
Disability status	.077	.001		.083	<.001	
HADS Depression	.135	<.001		.104	<.001	
BMI	-.010	.656		-.012	.600	
Baseline heart rate	.019	.422	.438	-.045	.064	.389
Heart rate reactivity	-.056	.018	.003	-.078	.002	.005

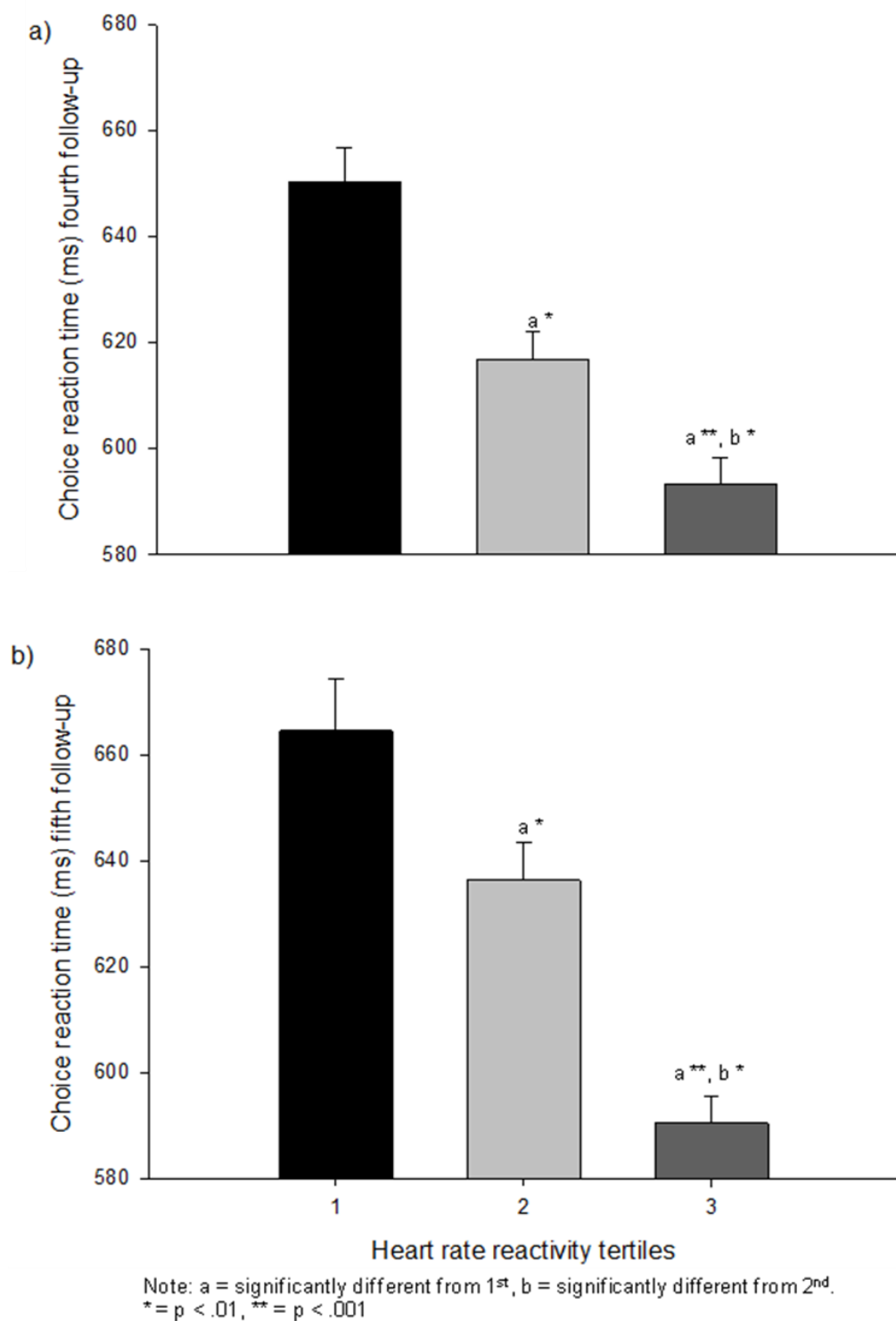


Figure 6.2. a) CRTs at the fourth follow-up by tertiles of heart rate reactivity, b) CRTs at the fifth follow-up by tertiles of heart rate reactivity

Cardiovascular reactivity and future AH-4 performance scores and CRT 12 years later

In the unadjusted model, HR reactivity was associated with AH-4 performance scores at the fifth follow-up, $\beta = .21, p < .001, \Delta R^2 = .046$; lower HR reactivity was again associated with poorer cognitive ability 12 years later. SBP ($p = .99$) and DBP ($p = .35$) was not significantly associated with future AH-4 scores. In the fully adjusted model, HR reactivity was still positively associated with AH-4 scores, $\beta = .130, p = <.001, \Delta R^2 = .015$. The final regression is shown in Table 6.3. Neither SBP ($p = .14$) nor DBP ($p = .41$) reactivity were associated with future AH-4 scores in this model. The unadjusted association with HR reactivity is again illustrated by plotting AH-4 scores against tertiles of reactivity (Figure 6.1b). AH-4 scores varied significantly with tertiles of HR reactivity, $F(2,1145) = 27.73, p < .001, \eta^2 = .046$. HR reactivity was negatively associated with CRT 12 years later in the unadjusted model, $\beta = -.177, p < .001, \Delta R^2 = .031$. SBP ($p = .25$) and DBP ($p = .86$) were not. In the fully adjusted model, HR reactivity was still associated with CRT, $\beta = -.078, p = .002, \Delta R^2 = .005$. The associations between SBP ($p = .74$) and DBP ($p = .50$) and future CRT were still not significant. The final regression is shown in Table 6.4. The unadjusted association between HR reactivity and CRT at the fifth follow-up is illustrated in Figure 6.2b. CRT varied significantly between the tertiles of HR reactivity, $F(2,1186) = 24.93, p < .001, \eta^2 = .040$.

Cardiac reactivity and future numerical and verbal reasoning ability

In the fully adjusted model, HR reactivity was positively associated with both AH-4 numerical and AH-4 verbal reasoning scores at the fourth follow-up, $\beta = .107, p < .001, \Delta R^2 = .010$, and $\beta = .076, p = .006, \Delta R^2 = .005$, and the fifth follow-up, $\beta = .150, p < .001, \Delta R^2 = .020$, and $\beta = .096, p < .001, \Delta R^2 = .008$, respectively.

Cardiovascular reactivity predicting future change in cognitive ability

In order to examine the association between reactivity and individual differences in change in cognitive ability over time, models were tested with AH-4 score or CRT at the fifth follow-up as the dependent variables and cardiovascular reactivity as the independent variable, with the earlier, fourth follow-up, AH-4 score or CRT, respectively, entered as a covariate. HR reactivity was associated with change in AH-4 score from the fourth to the fifth follow-ups, $\beta = .110$, $p < .001$, $\Delta R^2 = .012$. There were no associations for either SBP ($p = .74$) or DBP ($p = .98$). In the model that additionally adjusted for all the other covariates, HR reactivity was still associated with change in AH-4 scores, $\beta = .042$, $p = .01$, $\Delta R^2 = .002$. HR reactivity was also associated with CRT at the fifth follow-up after adjusting for CRT at the fourth follow-up, $\beta = -.065$, $p = .004$, $\Delta R^2 = .004$. Again, there were no analogous associations for SBP ($p = .51$) and DBP ($p = .72$). The association between HR reactivity and CRT change was still significant in the fully adjusted model, $\beta = -.057$, $p = .01$, $\Delta R^2 = .003$. Change in AH-4 score and CRT between the fourth and fifth follow-up was calculated by simple subtraction. Incidentally, the same results as those reported above emerge from fully adjusted regression models for HR reactivity when the dependent variables were the AH-4 ($p = .01$) and CRT ($p = .01$) change scores. To illustrate the HR reactivity associations, change scores for AH-4 and CRT were compared for tertiles of HR reactivity. Whereas change in AH-4 between the two follow-ups was not significant ($p = .35$), change in CRT was, $F(2, 1035) = 6.88$, $p = .001$, $\eta^2 = .013$, the highest tertile of HR reactors showed less decline in CRT over time. The summary data are presented in Figure 6.3a and 6.3b.

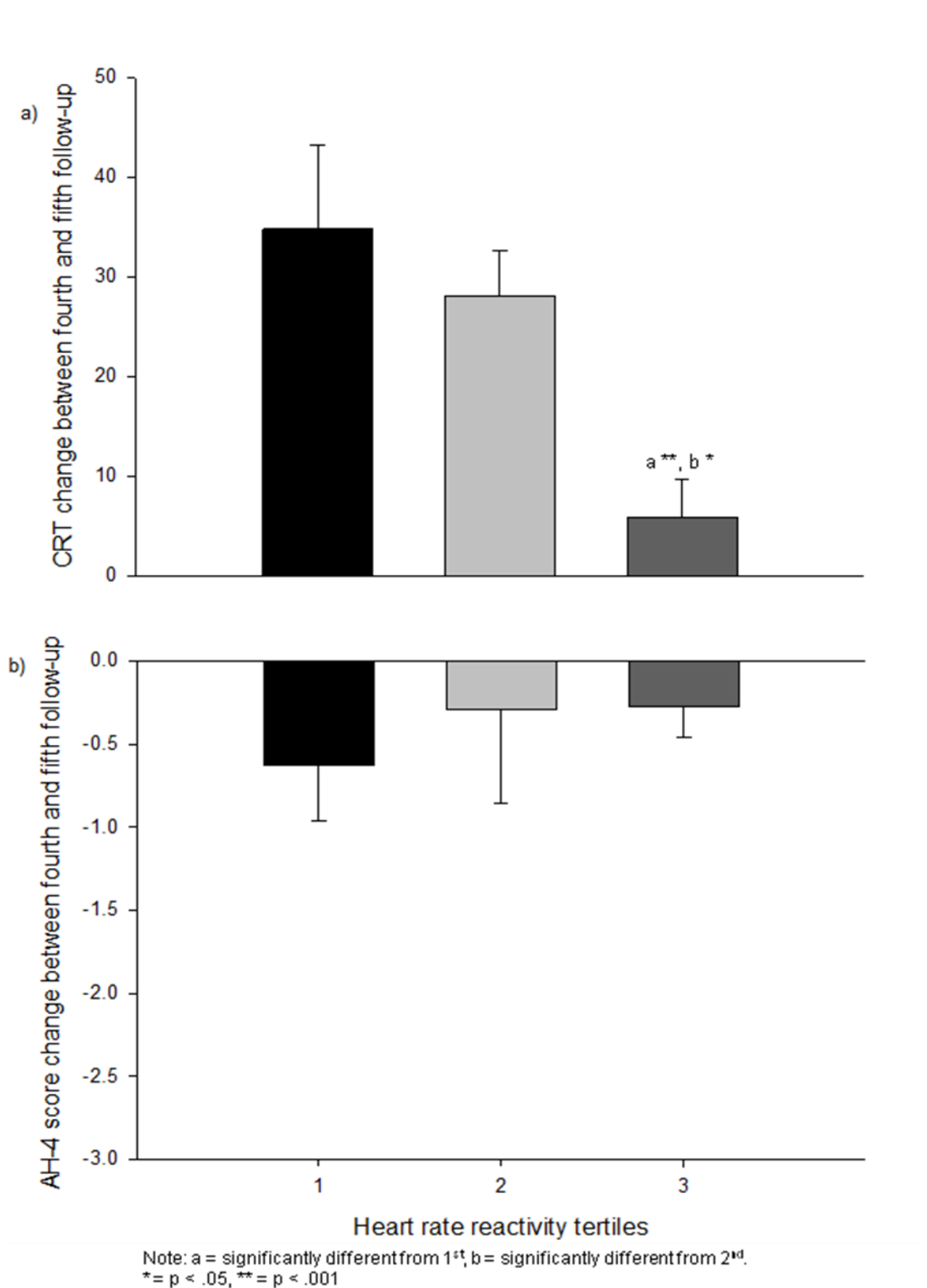


Figure 6.3. a) CRT change between fourth and fifth follow-up by tertiles of heart rate reactivity, b) AH-4 change score between fourth and fifth follow-up by tertiles of heart rate reactivity

Finally, in a supplementary analyses using ANCOVA, we analysed the effect of the interaction between tertiles of HR reactivity and age cohort on change in cognitive ability between the two follow-ups: these analyses were fully adjusted. For CRT, but not AH-4 scores, there was a significant reactivity x cohort interaction, $F(4, 1000) = 2.44$, $p = .04$, $\eta^2 = .010$. This is illustrated in Figure 6.4 which plots the change in CRT for tertiles of HR reactivity separately for the three age cohorts. As can be seen, the effect of tertiles of reactivity on CRT change is concentrated in the older cohort.

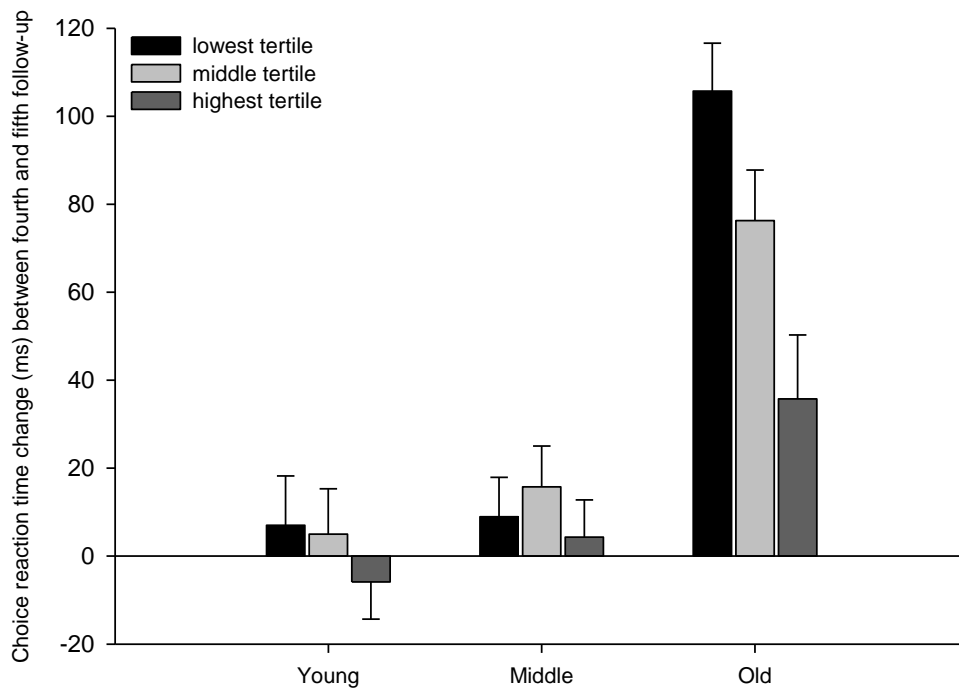


Figure 6.4. CRT change between fourth and fifth follow-up for tertiles of HR reactivity separately for the three age cohorts

Discussion

This study examined the association between cardiovascular reactivity and future cognitive ability, as indexed by scores on the AH-4 test of verbal and future numerical reasoning and by CRT. Both are accepted measures of cognitive ability (Deary et al., 2001; Rabbit &

Goward, 1994). The two measures were strongly, but imperfectly correlated at both follow-ups. Low, not high, HR reactions to acute stress were associated with low AH-4 test scores and longer CRTs five and 12 years later. Blood pressure reactivity was not associated with cognitive ability at either time point. Post hoc analyses of tertiles of HR reactivity indicated a dose-response relationship between cardiac reactivity and AH-4 scores and CRT at both follow-ups; blunted HR reactivity was associated with poorer future cognitive ability. HR reactivity was positively associated with both the numerical and verbal reasoning components of the AH-4. These associations between HR reactivity and cognitive ability remained statistically significant in regression models that adjusted for age cohort, sex, household occupational group, disability status, depressive symptomatology, BMI, and baseline HR.

Additionally, HR reactivity was associated with change in cognitive ability over time, i.e., low HR reactivity was associated with poorer AH-4 scores and slower CRTs at the fifth follow-up even after statistical adjustment for cognitive ability at the fourth follow-up, seven years earlier. This suggests that low HR reactivity may be a marker of cognitive aging. Cognitive aging refers to age-related decrements in cognitive function. It would appear that inflammatory markers, such as c-reactive protein (Deary et al., 2009; Weaver et al., 2002; Yaffe et al., 2003) and IL-6 (Deary et al., 2009; Rafnsson et al., 2007; Yaffee et al., 2003), are not only associated with cognitive ability but predict cognitive aging.

Increased systemic oxidative stress has also been reported to amplify cognitive aging (Berr, Balansard, Arnaud, Roussel, & Alperovitch, 2000; Coyle & Puttafarcken, 1993; Whalley, Deary, Appleton, & Starr, 2004). The present study is the first we know of to find that HR reactivity may also be a predictor of cognitive aging. However, it should be conceded that general intelligence measures are fairly stable over time (Conley, 1984) and, accordingly, may afford less than optimal measures of short term cognitive aging. Further, it has been

argued that cognitive aging is mainly accounted for by a decline in inspection time and CRT (Nettelbeck & Rabbitt, 1992). In the present study, the mean AH-4 scores were virtually identical at the two follow-ups, whereas CRT lengthened by 2% between the fourth and fifth follow-ups. Thus, we would expect that if HR reactivity is a marker of cognitive aging, associations would be stronger with CRT as the outcome. Our supplementary analyses were supportive. High HR reactors showed less of a lengthening in CRT over seven years than the rest of the sample; the analogous effect for AH-4 scores was not statistically significant. Finally, the effects of tertiles of reactivity on change in CRT was concentrated in the oldest cohort. This is perhaps hardly surprising, given that it is in this cohort that cognitive aging should be most evident.

The observed negative association between cognitive ability and reactivity is in line with that observed in two earlier studies, which found that lower cardiovascular reactivity was associated with poorer performance on the mental stress task (DeGangi et al., 1991; Duschek et al., 2009). However, it should be conceded that two other studies including a sizable study in older adults failed to find an association between reactivity and cognitive ability as revealed by performance on the stress task (Bucks & Seljos, 1994; Wright et al., 2005). Nevertheless, the present study is the largest study by some considerable margin to address this issue. In addition, the negative association observed in the present study is consistent with a recent analysis of the oldest cohort in this sample revealing a positive retrospective association between AH-4 scores and HR reactivity seven years later (Ginty et al., 2011). However, this is the first study we know of that links HR reactivity to future cognitive ability. Taken together, our analyses indicate an intimate association between HR reactivity and cognitive ability across the life course. Nevertheless, problems of causation and the direction of causation remain. What the present analyses indicate is that a causal pathway from poor cognitive ability to low reactivity is not the only possibility,

but that the link between cognition and reactivity may be bi-directional. Deliberations on causality would have undoubtedly been helped had reactivity been measured at more than one time point and cognitive ability at all time points in the full sample. Unfortunately, as with all the large scale epidemiological studies which measure reactivity, this was not feasible. However, it is worth noting that cardiovascular reactivity has been found to be reasonably stable over time, even across periods of 18 years (Hassellund, Flaa, Sandvik, Kjeldsen, & Rostrup, 2010). Determining causality even in prospective studies is fraught with pitfalls even when a substantial number of variables have been statistically controlled for (Christenfeld, Sloan, Carroll, & Greenland, 2004). It is possible that some third factor contributes to both cognitive ability and reactivity across the lifecourse. A candidate here may be central motivational dysregulation. By central motivational dysregulation we mean the suboptimal functioning of those systems in the brain, converging at the striatum and ventromedial prefrontal cortex, which appears to shape the motivation of our behaviour.

Our results are certainly consistent with the contention that relatively low cardiovascular reactions to acute stress may be a peripheral marker of central motivational dysregulation (Carroll et al., 2009a; Carroll et al., 2011). The circuits converging in the striatum and the ventromedial prefrontal cortex may be precisely those that support physiological reactivity (Carroll et al., 2009a; Carroll, 2011). As cognitive performance requires the integrity of such motivational systems (Busato, Prins, Elshout, & Hanmaker, 2000; Dweck, 1986; McClelland, Atkinson, Clark, & Lowell, 1953; Pintrich & Schunk, 1986), it would be expected that lower rather than higher cardiovascular reactivity would be associated with poorer subsequent cognitive ability, which is precisely what was observed for HR reactivity. Although speculative, it is possible that age-related functional deterioration of

central motivational systems, to an extent, underpins the link between HR reactivity and cognitive aging.

Our observations are also consistent with a growing body of cross-sectional and prospective evidence that low, not high, cardiovascular reactivity, including HR reactivity, is associated with a range of adverse health and behavioural outcomes, such as obesity (Carroll et al., 2008; de Rooij, et al., in press), symptoms of depression (Carroll et al., 2007; de Rooij, Schene, Phillips, & Roseboom, 2010; Phillips, Der, Hunt, & Carroll, 2011; York et al., 2007), tobacco and alcohol dependence, as well as risk of dependence (al' Absi, 2006; al' Absi, Hatsukami, & Davis, 2005; Girdler, Jammer, Jarvik, Soles, & Shapiro, 1997; Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Pankin, Dickensheets, Nixon, & Lovallo, 2002; Phillips et al., 2009; Roy, Steptoe, & Kirschbaum, 1994), and exercise dependence (Heaney, Ginty, Carroll, & Phillips, 2011). Thus, it would appear that for health outcomes such as high blood pressure, hypertension, and atherosclerosis cardiovascular reactivity is a positive predictor, whereas other outcomes are negatively associated with cardiovascular reactivity. This suggests that there might be an inverted U-shaped relationship such that very high and very low reactivity are maladaptive (Carroll et al., 2009a).

The present study is not without limitations. First, it should be acknowledged that the observed effect sizes are small. However, our effects are of the same order as the positive associations between cardiovascular reactivity and future resting blood pressure in this sample (Carroll, Ring, Hunt, & Ford, 2003), as well as those observed in other prospective studies of reactivity and subsequent blood pressure status (Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll, et al., 2001; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999)

and revealed by a recent meta-analysis (Chida & Steptoe, 2010). Second, given the oral response mode in the PASAT, cardiovascular perturbations could be attributed to speech. However, similar levels of HR reaction to mental arithmetic with and without a speech component have been reported (Sloan, Korten, & Myers, 1991) and we have reported substantial cardiovascular reactions to the PASAT when the mode of response was manual rather than oral (Carroll, Phillips, & Balanos, 2009; Balanos et al., 2010). Third, only blood pressure and HR reactivity were measured. It could have proved instructive to have a more comprehensive assessment of haemodynamics, such as that afforded by impedance cardiography. Further, a continuous rather than an intermittent of blood pressure and HR would have allowed us to chart the time course of acute stress reactivity, allowing us to represent cardiac reactivity as interbeat interval rather than HR. However, the decision to test participants in their own home and the size of the sample precluded more sophisticated measurement. An important distinction is made between cardiac and vascular reactivity in terms of both task and individual specificity (Kamarck, Jennings, Pogue-Geile, & Manuck, 1994). It is important to concede that it was only cardiac reactivity that was consistently linked to AH-4 scores and CRT in the present study. There were no consistent associations between blood pressure reactivity and future cognitive ability. Cardiac reactivity would appear to reflect both β -adrenergic and parasympathetic influences (Balanos et al., 2010; Sloan et al., 1991). Thus, low cardiac reactivity could reflect reduced β -adrenergic drive or less of a reduction in vagal tone during the stress task. Regrettably, in the present study we cannot determine which of these was the predominant mechanism for low cardiac reactivity. However, β -adrenergic blockade has been observed to attenuate cardiac reactivity, but not blood pressure reactivity (Winzer et al., 1999). Thus, reduced β -adrenergic drive would certainly accord with the present pattern of associations. Fourth, the absence of measures of subjective stress and task engagement

constitute another limitation, as it means we cannot fully rule out, as an explanation of the current results, the possibility that those with lower cognitive ability tended to disengage from what it is a cognitively challenging stress task. However, it seems to us equally possible that those with lower cognitive ability would have experienced more subjective stress when confronted with a difficult and challenging task.

In conclusion, we observed a positive association between HR reactivity and cognitive ability measured five and 12 years later. Reactivity was also associated with the relative change in cognitive ability over time; those with high HR reactivity were less likely to show relative cognitive decline. Our results are consistent with the notion that high cardiovascular stress reactivity may not necessarily be maladaptive and that low or blunted reactivity may also have negative corollaries.

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Chapter 7

Neural Corollaries of Exaggerated and Blunted Stress Reactivity

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Neural corollaries of exaggerated and blunted cardiac stress reactivity.

Abstract

Recent evidence suggests that blunted cardiovascular reactions to stress may have adverse consequences for health and behaviour and it has been proposed that blunted cardiovascular reactions to stress are a marker of dysregulation in areas of the brain associated with motivation. The present study aimed to identify the neural differences between pre-determined exaggerated and blunted cardiac reactors to acute psychological stress exposure. Seventeen participants (N = 8 exaggerated reactors; N = 9 blunted reactors) subsequently participated in a fMRI laboratory session examining brain activation to well-established stress and control task conditions. Exaggerated cardiac reactors exhibited significant increases in heart rate from control to stress, whereas blunted reactors showed no reaction. Blunted cardiac reactors displayed blunted activation in the mid anterior cingulate cortex (aMCC) and insula compared to exaggerated cardiac during the stress phase, and a deactivation in the amygdala. The biological differences between groups in response to the stress task could not be explained by subjective measures of engagement, stressfulness, or difficulty. This study supports the notion that blunted peripheral physiological stress reactivity may be a marker of some form of unconscious biological disengagement in those areas that support motivated behaviour.

Keywords: Heart rate, Stress reactivity, fMRI

There has been a long-standing consensus among researchers that individuals who show large magnitude cardiovascular reactions to acute psychological stress are at increased risk of developing cardiovascular disease. In support of this consensus, a number of large scale cross-sectional and prospective observational studies that show a positive association between the magnitude of cardiovascular reactions to acute psychological stress tasks and future blood pressure status and hypertension (Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll et al., 2001; Everson, Kaplan, Goldberg, & Salonen, 1996; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993; Newman, McGarvey, & Steele, 1999; Treiber, Turner, Davis, & Strong, 1997), markers of systemic atherosclerosis (Barnett, Spence, Manuck, & Jennings, 1997; Everson et al., 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Matthews et al., 1998), and left ventricular mass and/or hypertrophy of the heart (Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Kapuku et al., 1999; Murdison et al., 1998). Further, both qualitative reviews and meta-analyses have confirmed the consistency of this evidence, showing that exaggerated stress reactions reliably signal poor future cardiovascular health (Chida & Steptoe, 2010; Gerin et al. 2000; Schwartz et al., 2003; Taylor, Kamarck, & Dianzumba, 2003; Treiber et al., 2003).

Conversely, blunted reactivity to acute stress has been inferred to represent a benign or even protective pattern of cardiovascular responsivity among individuals. However, recent evidence suggests that blunted cardiovascular and/or cortisol reactions to stress may also have serious consequences for health and behaviour. For example, blunted cardiovascular and cortisol reactions to acute psychological stress characterize both smokers (al'Absi, Wittmers, Erickson, Hatsukami, & Crouse, 2003; Kirschbaum, Strasburger, & Langkrar, 1993; Phillips,

Der, Hunt, & Carroll, 2009) and those with alcohol and other substance addictions (Lovallo, Dickensheets, Myers, Thomas, & Nixon, 2000; Panknin, Dickensheets, Nixon, & Lovallo, 2002). Indeed, blunted stress reactions predict relapse in smokers who have quit (al'Absi et al., 2006; al'Absi, Hatsukami, & Davis, 2005) and are also evident in the adolescent offspring of alcoholic parents (Moss, Vanyukov, Yao, & Kirillova, 1999; Sorocco, Lovallo, Vincent, & Collins, 2006), suggesting that blunted stress reactivity may have prognostic value. Blunted cardiovascular and cortisol stress reactions are also characteristic of symptoms of bulimia (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012a) and exercise addiction (Heaney, Ginty, Carroll, & Phillips, 2011). In addition, recent epidemiological evidence shows that blunted cardiovascular and/or cortisol reactivity is associated with obesity, symptoms of depression, and poor self-reported health, and indeed predicts the likelihood of becoming obese (Carroll, Phillips, & Der, 2008), depressed (Carroll, Phillips, Hunt, & Der, 2007; de Rooij, Schene, Phillips, & Roseboom, 2010; Phillips, Hunt, Der, & Carroll, 2011), and subjectively unhealthy (De Rooij & Roseboom, 2010; Phillips, Der, & Carroll, 2009).

Although it may be premature to try to integrate these varied correlates of blunted stress reactivity, it is possible that they all, to different extents, reflect problems in appropriate goal-directed behaviour and motivation. Accordingly, it has been proposed that blunted physiological stress reactivity may be a peripheral marker of central motivational dysregulation (Carroll, Lovallo, & Phillips, 2009; Carroll, Phillips, & Lovallo, 2011; Lovallo, 2011). By central motivational dysregulation we mean the suboptimal functioning of those systems in the frontolimbic regions of the brain that support motivation. Many of the behavioural and health correlates of blunted stress reactivity would seem to be characterized by hypoactivation of these regions. Evidence shows decreased brain activation during

functional magnetic resonance imaging (fMRI) tasks in participants at risk for (Mannie, Taylor, Harmer, Cowen, & Norbury, 2011) and with depression (Holsen et al., 2011), at risk for (Andrews et al., 2011; Glahn, Lovallo, & Fox, 2007) and with alcoholism (Beck et al., 2009), and with bulimia (Joos et al., in press; Marsh et al., 2011). Hypoactivation was also observed in those with obesity (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008), weight gain (Stice, Yokum, Blum, & Bohon, 2010) and higher body mass index (Batterink, Yokum, & Stice, 2010). These studies observed responses to stimuli aimed at provoking activation of the frontolimbic regions of the brain (e.g. go/no go tasks and provocative images).

However, the neural corollaries of individual differences in cardiovascular stress reactivity have received scant attention. Nevertheless, there is preliminary evidence that individuals who show blunted cardiovascular stress reactions also show hypoactivation in limbic regions during stress exposure. Individual differences in blood pressure reactivity to stress has been reported to relate to differences in activation in the perigenual and mid-anterior regions of cingulate cortex (Gianaros, Derbyshire, May, Siegle, Gamalo, & Jennings, 2005), the posterior cingulate cortex (Gianaros, May, Siegle, & Jennings, 2005), and the amygdala (Gianaros et al., 2008). For example, in a study that examined the neural responses, using fMRI, to a standard stress task of eight high and low blood pressure reactors, selected on the basis of previous systolic blood pressure reactions during stress exposure, low reactors showed less activation in the posterior cingulate cortex when exposed to stress (Gianaros et al., 2005). At the time this study was conducted, however, nothing was known about the health and behavioural correlates of blunted stress reactivity and so the study's theoretical interest was very much directed at the neural correlates of exaggerated peripheral stress responses.

Given the paucity of research examining the neural corollaries of exaggerated and blunted cardiovascular stress reactivity, the present study compared the neural, using fMRI, and heart reactions to a standard stress task of extreme exaggerated and extreme blunted cardiac reactors, selected from a number of our previous laboratory studies of stress reactivity. It was hypothesized that blunted cardiac reactors would show less activation in the limbic regions of the brain.

Methods

Participants

Twenty-two healthy male undergraduate and postgraduate students (11 exaggerated and 11 blunted cardiac reactors) were recruited. Their mean (SD) age was 20.9 (1.56) years and their mean (SD) body mass index was 23.0 (1.52) kg/m². The high and low reactors did not differ in terms of age ($p = .96$) or BMI ($p = .40$). None of the participants smoked, and none had a history of cardiovascular disease, a current endocrine or immune disorder, an acute infection or another chronic illness, nor were any of the participants taking prescribed medication. All participants provided informed consent and the study was approved by the University of Birmingham Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Selection of participants

Ten (4 exaggerated and 6 blunted reactors) participants were selected from a temporal stability study in which cardiac reactions to a mental stress task, a 10-minute version of the paced auditory serial arithmetic test (PASAT; Gronwall, 1977), were measured using Doppler Echocardiography and electrocardiography on four separate occasions. A full description of

the version of the PASAT used is provided elsewhere (Ginty et al., 2012). Briefly, participants were presented with a series of single digit numbers and required, in each case, to add any given number to the number previously presented and call out the answer. The intervals between the numbers were 4.5 seconds for the first 2 minutes and shortened by .5 seconds every subsequent 2 minutes. The task also involved elements of competition, harassment, and social evaluation. As can be seen in Figure 7.1a and 7.1b, the exaggerated cardiac output and heart rate reactors, although showing some adaptation of response over sessions, remained high reactors throughout; the blunted reactors continued throughout to show low cardiac responses.

Ten further participants (5 exaggerated and 5 blunted cardiac reactors) were recruited from a study examining the inter-task consistency of cardiac stress responses, using the same measurement techniques as above. Since the PASAT is unsuitable for the fMRI part of the study, cardiac reactions to the PASAT were compared to reactions to a fMRI compatible task, the modified Multi Source Interference Task (MSIT; see later for description). The cardiac reactions of 48 participants were examined to the PASAT and MSIT, presented in a counter-balanced order. Although the PASAT elicited stronger reactions than the MSIT, $t(47) = 5.03$, $p < .001$ and $t(47) = 6.26$, $p < .001$, for cardiac output and heart rate reactivity respectively, reactions to the two tasks were highly correlated: $r(46) = .61$, $p < .001$ and $r(46) = .56$, $p < .001$, for cardiac output and heart rate reactivity respectively. The remaining two participants (2 exaggerated reactors) were recruited from a heart rate reactivity study conducted by colleagues. The HR reactions to the PASAT of these two participants were 45 and 33 beats per minute.

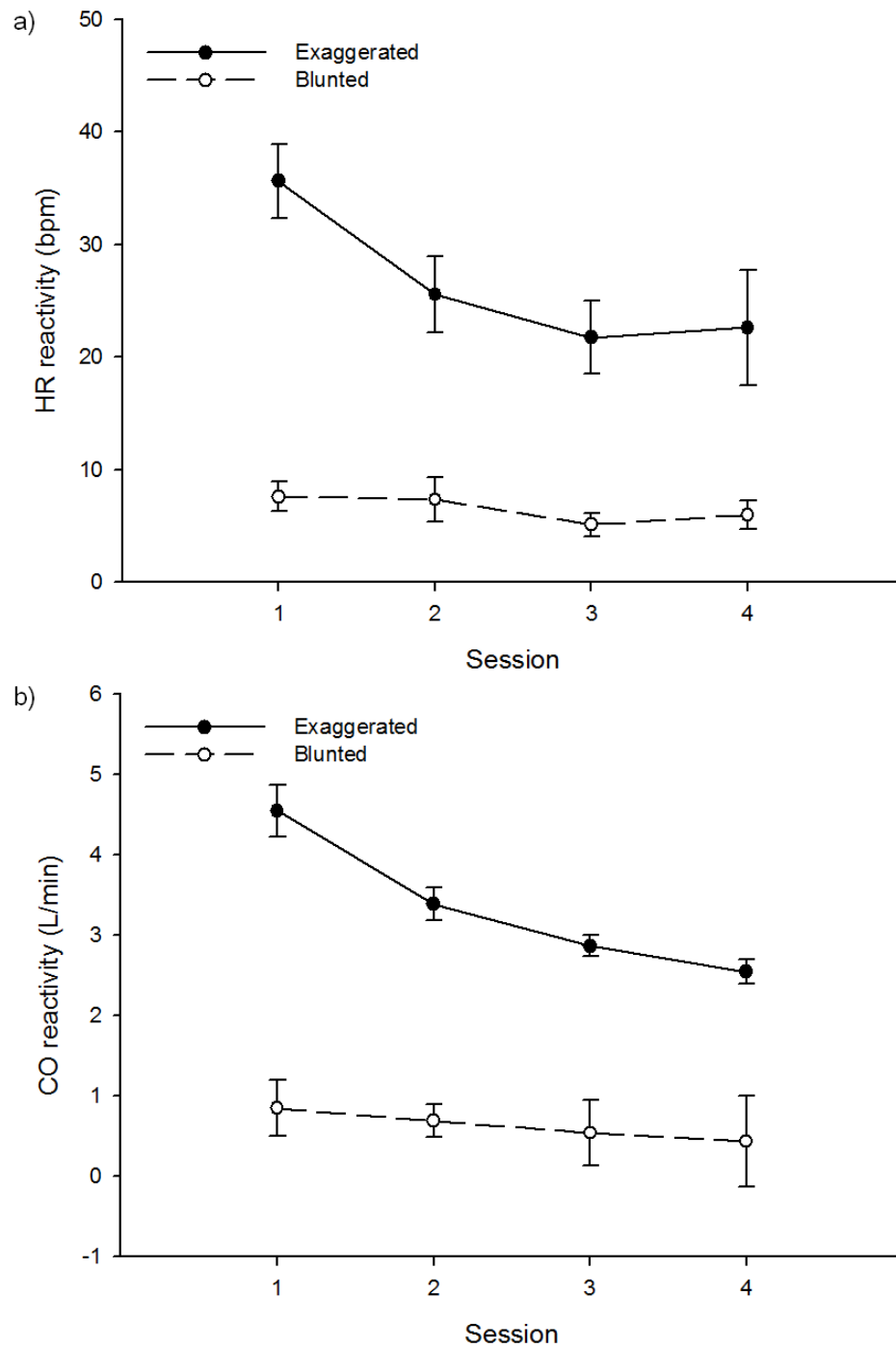


Figure 7.1a. Heart rate reactivity of extreme exaggerated and blunted reactors over four independent laboratory sessions.

Figure 7.1b. Cardiac output reactivity of extreme exaggerated and blunted reactors over four independent laboratory sessions

Multi source interference task

The MSIT (Bush & Shin, 2006; Gianaros et al., 2009) comprised of two conditions: a congruent condition and an incongruent condition. The two conditions, each lasting 52-60 seconds were administered in a blocked design, and each was preceded by a 10-17 second rest period where participants fixated on a crosshair. In both MSIT task conditions participants were presented with three numbers in single trials; one number was different to the other two which were identical. Participants selected the different number by pressing one of three buttons on a fMRI compatible response box. For all trials in the congruent condition, the different number in the display appeared in a location that was aligned with its spatial position on the response box. Thus, there was a one-to-one correspondence between the stimulus position and the correct response option. For the incongruent trials, the different number, was incongruent to its spatial location on the response box, such that there was now no alignment between the stimulus position and the correct response option. In this condition, performance was titrated and maintained at *circa* 60% correct by adjusting the inter-trial intervals. For each of three trials, the incongruent and congruent conditions were each presented four times in an alternating order, separated by the resting crosshair condition; the incongruent condition always preceded the congruent condition. In all, the task lasted 9 minutes and 20 seconds. A fuller description of this task is provided elsewhere (Gianaros et al., 2009; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, in press).

Procedure

The selected exaggerated and blunted reactors were required to abstain: from alcohol 12 h, vigorous exercise 12 h, caffeine 2 h, and food and drink other than water 1 hour before fMRI testing. Participants were tested between 11am and 3pm at the Birmingham University

Imaging Centre. On arrival at the imaging centre, they were provided with a description of the experiment and familiarized with the fMRI equipment. Participants were instrumented for the non-invasive measurement of heart rate using a MRI compatible pulse oximeter (InVivo 4500 MRI; Invivo Research Corp., Orlando, FL, USA) which was recorded throughout. As indicated above, participants were studied in the fMRI under three conditions: rest, congruent MSIT, and incongruent MSIT. The first of these conditions allowed the acquisition of structural MRI images (for approximately 8 minutes). The last of these conditions served as the stress task exposure whereas the congruent version of the MSIT served as the non-stress control. At the end of the fMRI session, participants completed a brief questionnaire rating how difficult, stressful, and engaging they found the stress task, as well as how well they thought they performed on the task and how stressful they found being in the fMRI scanner; responses were made on a 7-point Likert scale in which 0 indicated “not at all” and 6 indicated “extremely.”

Structural and functional magnetic resonance imaging acquisition

Neuroimaging data were acquired using a Philips 3 T Achieva system. Structural images were acquired using T1T2E technique (TR=8.4, FoV=232 mm, flip angle=60° 288x288 matrix, 175 slices). Blood oxygenated level dependent (BOLD) contrast weighted echoplanar images (EPI) were generated (repetition time TR=3000 ms, echo time TE=3500 ms, FoV=220mm, 52 slices, 3.0 isotropic voxels) during functional scans. Participants completed the MSIT during functional scans as detailed above.

Data pre-processing

The object of the analysis was to describe BOLD response in the high and low reactors and compare differences in BOLD response between the exaggerated and blunted reactors during

performance of the MSIT. To make these calculations the following pre-processing procedures were performed using statistical parametric mapping software (SPM8; Wellcome Trust Centre for the Study of Cognitive Neurology, www.fil.ion.ucl.ac.uk/spm). Slice timing correction was used to correct for the time difference in slice acquisition. Head movement between scans was corrected by aligning all subsequent scans with the first and an unwarp function applied to minimise artifacts from the head motion. Each realigned set of scans from every subject was co-registered with their own hi-res structural MRI image and then reoriented into the standardized anatomical space of the average brain provided by the Montreal Neurological Institute. To increase the signal to noise ratio and accommodate variability in functional anatomy, each image was smoothed in X, Y, and Z dimensions with a Gaussian filter of 8 mm (FWHM).

Data analyses

Group (exaggerated and blunted cardiac reactors) differences in self report were examined using one-way ANOVAs. To provide summary heart rate data for analyses, heart rate values were averaged separately for each of the three conditions across the first two trials. The averages generated were then subject to a 2 groups (exaggerated and blunted reactors) x 3 conditions (rest, congruent, incongruent) ANOVA. Group by condition interactions were followed up with simple effects tests and pairwise comparisons between conditions for each group.

Assessment of regional brain activation

For each subject, a boxcar model with a hemodynamic delay function was fitted to each voxel to contrast the incongruent with congruent conditions and generate a statistical parametric map. Baseline drifts were removed by applying a high-pass filter. Contrast images for each

individual subject were then combined at the second level to generate maps indicating within and between group effects. This random effects implementation corrects for variability between subjects so that outlying subjects cannot drive the result. A whole brain grey matter mask was applied using WFU Pickatlas to exclude white matter and ventricles from the analysis. Brain regions with a large statistic correspond to structures whose BOLD response shares a substantial amount of variance with the conditions of interest. Images were thresholded at an arbitrary $p < 0.001$ with an extent threshold of 50 contiguous voxels, which provides a reasonable balance of protection against false-positive without artificially concealing the real profile of activation. *A priori* analyses of hypothesis-driven regions of interest (ROIs) involved examination of the insula and amygdala regions (Critchley et al., 2005; Gianaros et al., 2005), thresholds were set at $p < .05$ with an extent threshold of 10 contiguous voxels.

Results

Self-report and cardiac stress responses

Three exaggerated cardiac reactors and two blunted cardiac reactors data were excluded because of excessive movement artifacts in their functional neuroimaging data; thus, the final analyses included 17 participants (8 exaggerated reactors and 9 blunted reactors). There were no significant differences between high and low reactors in how difficult ($p = .39$), stressful ($p = .45$), or how engaging ($p = .45$) they found the MSIT task. There were also no group differences in how well they thought they performed ($p = .39$) or how stressful they found being in the scanner ($p = .53$). With regard to heart rate during the session, there was a significant main effect of condition (baseline, congruent, incongruent), $F(2, 30) = 13.45$, $p = .001$, $p\eta^2 = .473$, and a significant main effect of group, $F(1, 15) = 12.38$, $p = .003$, $p\eta^2 = .452$.

There was also a significant group x condition interaction, $F(2, 30) = 11.66, p = .002, \eta^2 = .437$. Pairwise comparisons revealed that high reactors increased slightly between baseline and the congruent ($p = .051$), and increased significantly between baseline and incongruent ($p = .001$) and between congruent and incongruent ($p < .001$). In contrast, the heart rate of low reactors did not change significantly between baseline and congruent, baseline and incongruent, and between congruent and incongruent ($p > 0.10$ in all cases). Figure 7.2 displays each group's average change from baseline to the congruent and incongruent conditions.

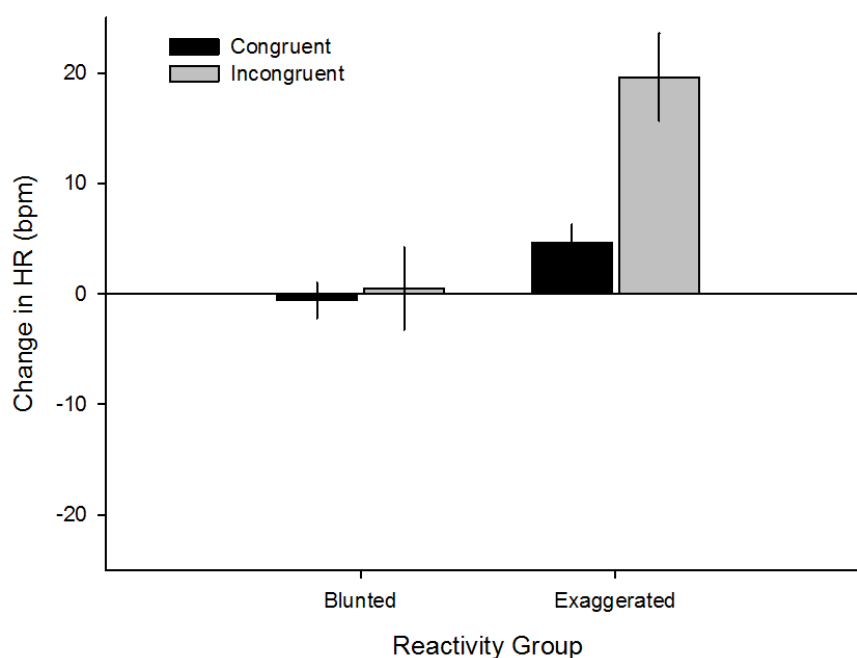


Figure 7.2. Change in heart from baseline to the congruent and the incongruent conditions for the MSIT for exaggerated and blunted cardiac reactors.

Exaggerated cardiac reactors condition-related brain activation and deactivation

Highly significant and relevant BOLD increases and decreases during the incongruent (stress) condition compared to the congruent (control) condition for exaggerated cardiac responders are shown in Table 7.1 and Table 7.2, respectively. During the stress condition, exaggerated

cardiac responders had significantly greater BOLD activation in the occipital and parietal lobe; these analyses survived family wise error corrections. There were significantly greater BOLD activation responses in several other areas including the brainstem, cerebellum, anterior mid cingulate cortex (aMCC), caudate, and inferior frontal gyrus. Exaggerated cardiac responders had significantly less BOLD activation during the stress condition compared to the control condition in the superior frontal gyrus, an effect which survived family wise error correction, and in the posterior cingulate cortex; thus, these areas showed evidence of de-activation during stress exposure. In addition to Tables 7.1 and 7.2, the outcomes for exaggerated cardiac reactors are illustrated in Figures 7.3 and 7.4.

Blunted cardiac reactors condition-related brain

Highly significant and relevant BOLD increases and decreases during the incongruent (stress) condition compared to the congruent (control) condition for blunted cardiac reactors are shown in Tables 7.1 and 7.2, respectively. BOLD increases were seen in the occipital and parietal lobes, and parahippocampal gyrus during the stress condition compared to the control condition, and the effects again survived family wise error correction. Additionally, there were significantly greater BOLD responses in other areas of the brain including the frontal lobe and the posterior cingulate cortex. There were several areas of the brain where blunted cardiac responders displayed decreases in BOLD responses to stress, i.e., greater activation during the control condition relative to the stress condition. Deactivation, surviving family wise error correction, was seen in the parietal and temporal lobes, and in the hippocampus. Deactivation also occurred in the amygdala, posterior cingulate cortex, superior frontal gyrus, and anterior cingulate. The outcomes are illustrated in Figure 7.3 and 7.4.

Table 7.1. Significant BOLD activation during incongruent (stress) compared to congruent (control) for exaggerated and blunted cardiac reactors, threshold $p < .001$, extent threshold 50 contiguous voxels.

Figure label	Side	Brain area	Exaggerated reactors			Blunted reactors		
			(x, y, z coordinates) region	Cluster size	t value	(x, y, z coordinates) region	Cluster size	t value
1	R	Medial premotor cortex	(6, 14, 58) BA 6	488	13.41	(36, 6, 58) BA 6	66	6.47
	L		(-32, -4, 66) BA 6	75	6.87	—	—	—
2	L	Anterior mid cingulate cortex (aMCC)	(0, 34, 26) BA 32	134	8.65	—	—	—
	R		(2, 18, 20)	134	5.12	—	—	—
3	L	Brainstem	(-12, 20, -4)	1554	9.87	—	—	—
	R		(14, -18, -6)	1554	9.20	—	—	—
4	R	Thalamus	(-9, -12, -2)	1554	7.81	(18, -22, 8)	474	9.35
5	R	Caudate	(32, -34, 4)	50	9.96	—	—	—
6	L	Posterior Cingulate Cortex	—	—	—	(-6, -24, 28) BA 23	133	12.73
	R		—	—	—	(8, 10, 32) BA 23	641	10.66
N/A	R	Insula	(38, 20, 16) BA 13	599	7.97	(44, 10, 16) BA 13	1452	10.91*

* ROI analyses of the insula revealed greater activation in exaggerated cardiac reactors during stress compared to rest, despite the peak voxel being higher in the blunted cardiac reactors.

Table 7.2. Significant BOLD deactivation during incongruent (stress) compared to congruent (control) for exaggerated and blunted cardiac reactors, threshold $p < .001$, extent threshold 50 contiguous voxels.

Figure label	Side	Brain area	High reactors			Low reactors		
			(x, y, z coordinates) region	Cluster size	t value	(x, y, z coordinates) region	Cluster size	t value
7	L	Ventral Posterior cingulate cortex (vPCC)	(-4, -50, 18) BA 30	78	5.97	(-8, -42, 36) BA 30	504	8.18
8	L	Medial frontal cortex	(-12, 58, 0) BA 10	482	5.96	(-10, 66, 26) BA 10	3207	11.34
9	L	Perigenual anterior cingulate cortex (pACC)	_____	_____	_____	(-16, 42, 2) BA 32	3207	9.42
10	R	Amygdala	_____	_____	_____	(-28, -12, -16)	80	13.75*
	L	Amygdala	_____	_____	_____	(20, -10, -10)	51	10.08
11	L	Temporal cortex	_____	_____	_____	(-50, -66, 26) BA 39	533	17.98*
	R		_____	_____	_____	(36, 10, -36) BA 38	131	11.00
						(-58, -12, -8) BA 21	52	8.72

*Survived family-wise error corrections.

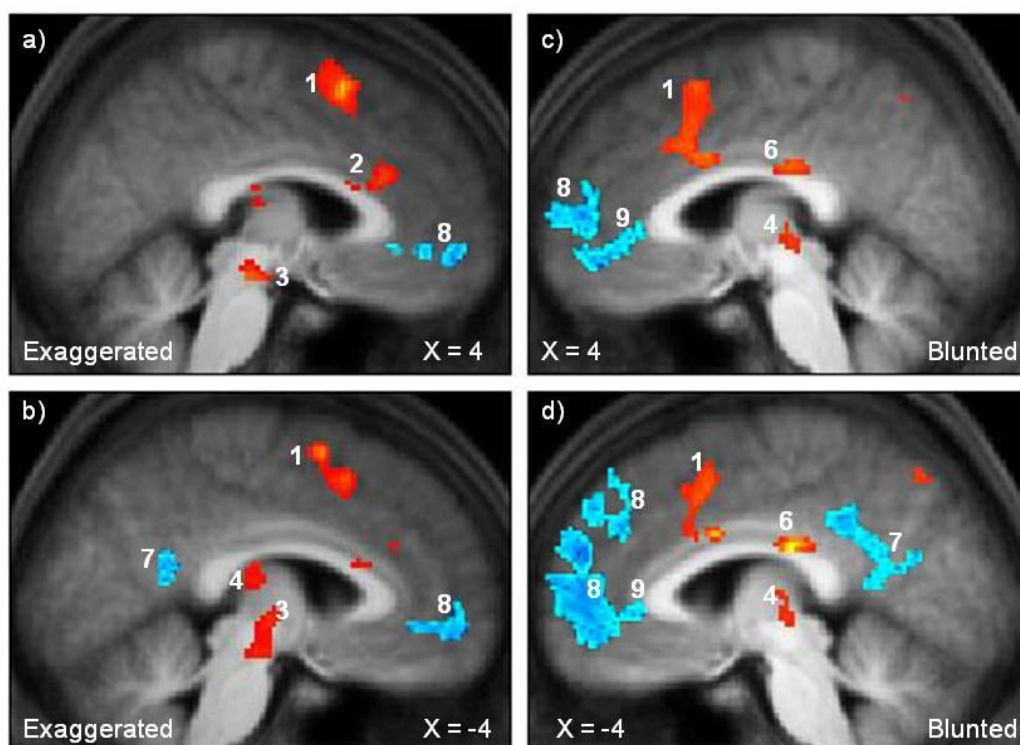


Figure 7.3. Sagittal slices showing BOLD activation (red) and deactivation (blue) during the incongruent stress condition in comparison to the congruent control condition for both exaggerated and blunted cardiac reactors.

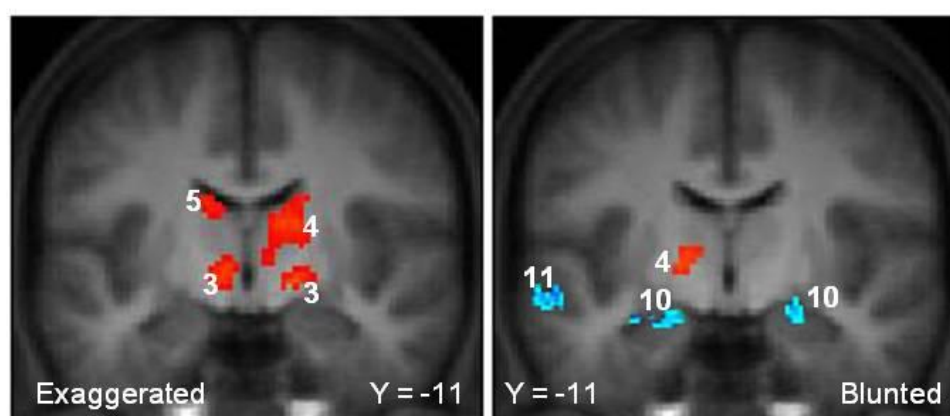


Figure 7.4. Coronal slices showing BOLD activation (red) and deactivation (blue) during the incongruent stress condition in comparison to the congruent control condition for both exaggerated and blunted cardiac reactors. Please refer to Tables 7.1 and 7.2 for figure labels.

Group differences in condition-related regional brain activity

A whole-brain ANOVA showed that exaggerated cardiac reactors also expressed greater activation of the aMCC (BA 24) during the incongruent compared with the congruent condition, group x condition cluster $F(1, 15) = 33.96, p < .001$, voxel contiguity threshold = 50 voxels (Figure 7.5). A priori analyses of ROIs revealed significant group x condition differences for the amygdala $F(1, 15) = 11.66, p = .004$ and for the insula $F(1, 15) = 11.37, p = .004$.

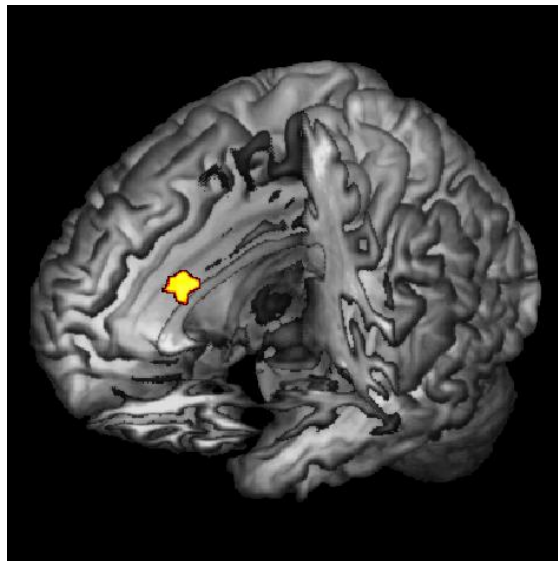


Figure 7.5. Group (Exaggerated, Blunted) x Condition (Incongruent, Congruent) BOLD activation differences using a whole brain exploratory analysis, threshold $p < .001$, extent threshold 50 contiguous voxels.

Discussion

The present study compared neural activation differences in pre-established exaggerated and blunted cardiac reactors. This is the first fMRI study to screen and select extreme cardiac reactors using Doppler echocardiography for cardiovascular measurements. As expected, during the fMRI testing session, exaggerated cardiac reactors displayed significant increases

in HR during the stress task compared to resting baseline, while low reactors' HR did not change with stress exposure. There were no significant differences between exaggerated and blunted reactors in how difficult, stressful, or engaging they found the task or in their subjective assessment of their performance of the task. This indicates that differences in HR reactivity and any potential differences in neural activation could not be attributed to simple expedients such as group differences in task involvement. Participants in the high and low reactor groups also did not differ in age or BMI.

The most notable difference between groups in neural activation during the stress task compared to the control condition was in the aMCC; exaggerated reactors experienced an increase in aMCC activation during the stress task while blunted reactors did not. There were also group differences in insula and amygdala responses to stress, confirming *a priori* hypotheses. Exaggerated reactors had greater activation in the insula during stress and in comparison blunted reactors exhibited hypo-activation. Blunted reactors also showed deactivation of the amygdala during stress, i.e., they showed greater activity in the amygdala during rest than during the stress task. Separate analyses examining the neural reactivity of each group separately demonstrated more widespread and intense activation in the exaggerated reactors during stress in the brain stem and cerebellum which blunted reactors did not show.. Both groups showed similar activation in the occipital and parietal lobes.

The results from the whole brain analyses are somewhat different than a previous study examining neural responses of high and low systolic blood pressure reactors during stress exposure (Gianaros et al., 2005), which found group differences in posterior cingulate activity. High reactors exhibited increases in activation in the posterior cingulate during stress exposure whereas low reactors showed decreases in the posterior cingulate. In the present

study, there were no differences between exaggerated and blunted cardiac reactors in the posterior cingulate during stress exposure. A potential explanation could reside in the selection of high and low reactors; Gianaros and colleagues selected extreme reactors based on systolic blood pressure, while the present study used CO and HR reactivity as selection criteria and used a stricter cut-off to identify extreme reactors. Additionally, participants in the present study were all relatively young compared with the participants in the previous study. It should be noted that despite the differences seen in group comparisons, overall the stress task elicited responses in similar areas of the brain (Gianaros et al., 2005).

A priori predictions regarding differential activation of the insula and amygdala during stress between the groups were confirmed. Evidence implicates the insula in cardiovascular regulation (Allen, Saper, Hurley, & Cechetto, 1991; Cechetto, 1994; Cechetto & Chen, 1990; Cechetto & Shoemaker, 2009; Oppenheimer, 1993; Ruggiero, Mraovitch, Granata, Anwar, & Reis, 1987; Verberne and Owens, 1998; Yasui, Breder, Saper, & Cechetto, 1991) and a recent meta-analysis consisting of cardiovascular stress reactivity neuroimaging studies identified the insula as one of three key regions associated with individual differences in stress-evoked cardiovascular reactions (Gianaros & Sheu, 2009). Group differences in the amygdala are also in line with previous studies which have demonstrated a relationship between the amygdala and cardiovascular control (Gianaros et al., 2008) and sympathetic arousal (Critchley, 2005; Bechara, Damasio, Damasio, & Lee, 1999). Additionally, fMRI studies have shown hypoactivation in the amygdala in individuals with depression (Holson et al., 2011) and at risk for alcoholism (Glahn et al., 2007), both of which have been related to blunted physiological reactions to stress (Carroll et al., 2007; Moss et al., 1999; Phillips et al., 2011; de Rooij et al., 2010; Salomon, Clift, Karslsdottir, & Rottenberg, 2009; Schwerdtfeger,

& Rosenkaimer, 2011; Sorocco et al., 2006). What is most notable about the current results is that blunted cardiac reactors showed less activity in the amygdala during stress than during baseline. It would appear that individuals who show blunted peripheral stress reactivity are also unresponsive in a key neural component of emotion. It is worth noting that individuals with a damaged amygdala are emotionally unresponsive (Adolphs et al., 2005; Buchanan, Etzel, Adolphs, & Tranel, 2006) and have impaired decision making and lower sympathetic reactivity when thinking about risky behaviour (Bechara et al., 1999). Blunted physiological reactions have been related to risky behaviours, such as addiction (Lovallo et al., 2000; Pankin et al., 2002) and impaired decision making such as reoffending among delinquent adolescents (de Vries-Bouw et al., 2011). The amygdala effects were modest, but nevertheless statistically significant. Research shows that tasks which involve non-emotional stimuli, such as the MSIT, show a stronger relationship between the anterior cingulate and sympathetic arousal than between the amygdala and sympathetic arousal (Bush et al., 2008; Bush & Shin, 2006; Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Critchley et al., 2003).

The most robust group differences were in the anterior cingulate, specifically the aMCC, which has also been related to cardiovascular activation in response to stress (Critchley et al., 2000; Critchley et al., 2003); higher cardiovascular reactors have been found by others to have greater aMCC activation during stress (Gianaros et al., 2005a). Just as high reactivity to stress has been related to cardiovascular disease, greater activation of the aMCC has been found in patients with cardiovascular disease (Soufer et al., 1998). Thus, it is perhaps not unexpected that exaggerated reactors in the present study displayed greater activation in the aMCC during stress than blunted reactors. That blunted cardiac reactors failed to show activation in the aMCC during stress compared to the control condition is in line with a previous studies

reporting that patients with damage to their anterior cingulate cortex displayed blunted autonomic arousal to cognitive and motor tasks (Critchely et al., 2003). Hypo-activation of the anterior cingulate has also been related to depression (Holson et al., 2011) and bulimia (Marsh et al., 2011; Joos et al., 2011), both of which are associated with blunted physiological reactions to stress (Carroll et al., 2007; Ginty et al., 2012; Koo-Loeb, Pederson, & Carroll, 1998; Moss et al., 1999; Phillips et al., 2011; de Rooij et al., 2010; Salomon et al., 2009; Schwerdtfeger, & Rosenkaimer, 2011; Sorocco et al., 2006).

The aMCC has also been implicated in higher cognitive functions such as cognitive information processing and executive function (Bush, Luu, & Posner, 2000; Bush et al., 2008; Bush et al., 2002; Critchley, 2003; Williams et al., 1998; Shima & Tanji, 1998; Paus, 2001). Recent studies indicate a link between poor cognitive ability and blunted peripheral physiological stress reactivity (Ginty, Phillips, Der, Deary, & Carroll, 2011a, Ginty, Phillips, Der, Deary, & Carroll, 2011b; Ginty, Phillips, Roseboom, Carroll, & de Rooij, 2012b). One of the measures of cognitive ability, choice reaction time, involves both cognitive processing and executive functioning and has been regarded as a marker of cognitive aging (Nettelbeck & Rabbitt, 1992). Results showed that blunted cardiac reactions to stress predicted a decline in choice reaction time amongst the oldest participants in the study over a seven year period (Ginty et al., 2011a). Evidence from the present study suggests that blunted neural activation to stress may also be related to cognitive ability and that some sort of biological disengagement is occurring across multiple systems in blunted reactors when confronted by a stressful and cognitively challenging stimulus.

It is widely accepted that the amygdala, insula, and anterior cingulate work together as a network to evaluate and process the motivational and emotional aspects of psychologically

stressful stimuli in the environment (e.g. aversive stimuli; uncontrollable stimuli); they then interact to elicit appropriate cardiovascular and motor responses (Bennarroch, 1997; Bush et al., 2000; Cechetto, 1994; Ongur & Price, 2000; Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Gianaros et al., in press; Gianaros & Sheu, 2009; Hagemann, Waldstein, & Thayer, 2003; Koski & Paus, 2000; Resstel & Correa, 2006; Thayer, & Lane, 2000; Wager et al., 2009). This network is vital for motivated behavioural responses and adaptations to the threat or challenge (Gianaros et al., in press; Dampney, 1994; Dampney et al., 2002). In the present study, participants with blunted cardiovascular reactions to stress displayed either blunted responses or deactivation in these areas of the brain when exposed to psychologically stressful stimuli. The current findings offer support to the hypothesis that blunted peripheral physiological reactions to acute psychological stress may be a peripheral marker for some form of dysregulation in those areas of the brain that are associated with motivation (Carroll et al., 2009; Carroll et al., 2011; Lovallo, 2011). Further, this biological disengagement may contribute to outcomes such as obesity, addiction (al' Absi et al., 2003; Lovallo et al., 2000), depression (Salomon et al., 2009; de Rooij et al., 2010), and other adverse behaviours (Ginty et al., 2012a). It is also worth noting that this biological disengagement is independent of participants' ratings of engagement with the stress task; such independence of self-report and biological measures has been observed previously (Ginty et al., 2012; Heaney et al., 2011).

The present study is not without limitations. First, all of the participants tested were males. However, there is no reason to believe the results would be any different if female participants were included (Balanos et al., 2010; Carroll, Turner, Lee, & Stephenson, 1984; Gianaros et al., 2005). Second, only HR was measured during the fMRI protocol. However, participants were initially selected using both CO and HR using Doppler echocardiography, a highly

sensitive and clinically accepted device (Balanos et al., 2010; Fellahi et al., 2009).

Additionally, HR was recorded continuously throughout the scanning session which allows for a more definitive assessment of the relationship between neural and cardiac responses (Gianaros et al., 2005). Third, it could be argued that individual differences in cardiac reactivity is not stable over time and, accordingly, the present findings may not be truly representative. However, the temporal stability of exaggerated and blunted reactivity was tested prior to fMRI testing, providing further evidence for the temporal stability of cardiac reactivity (Carroll et al., 1984) and the stability of both cardiovascular and neural reactions to the MSIT task (Sheu, Jennings, Gianaros, in press). Lastly, the sample size was relatively small. However, extreme groups were being examined and a large number of participants were screened to select these groups. In addition the sample size was similar in magnitude to other studies of this nature (Gianaros et al., 2005).

In summary, extreme blunted cardiac reactors displayed blunted activation in the aMCC and insula compared to exaggerated cardiac reactors during an acute stress task, and a deactivation in the amygdala. The biological differences between groups in response to stress task could not be explained by subjective measures of engagement, stressfulness, or difficulty. This study supports the notion that blunted peripheral physiological stress reactivity may be a marker of some form of unconscious biological disengagement in those areas of the brain that support motivated behaviour.

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Chapter 8

General Discussion

The overarching aims of the studies in present thesis were to better understand the behavioural, cognitive, and neural corollaries of blunted cardiovascular and/or cortisol reactions to acute psychological stress and further test the theory that blunted cardiovascular and cortisol reactions to acute psychological stress are markers of unconscious dysfunctioning in the motivational areas of the brain (Carroll, Lovallo, & Phillips, 2009). These aims were achieved by using a mixed methods interdisciplinary approach encompassing both laboratory studies and secondary analyses of epidemiological datasets.

Summary of Results

Responses to stress and exercise dependence

The aim of Chapter 2 was to examine cardiovascular and cortisol responses to stress in a group of young women who exhibited symptoms of exercise dependence, a non-substance abuse addiction. Ten women with the highest exercise dependence scores of questionnaire measures of dependence and ten control women, with low dependence symptom scores, underwent a standardised laboratory stress testing session. Those identified as having exercise dependence exhibited both blunted heart rate (HR) and cortisol reactions to the laboratory stress task. Given that the exercise dependence group was slightly fitter than the control group, and that high cardio-respiratory fitness is associated with lower cardiovascular reactivity (Forcier et al., 2006), the HR analysis was re-run adjusting for estimated cardio-respiratory fitness, calculated using an established algorithm (Jurca et al., 2005). The group differences remained significant. Additionally, the group differences in HR and cortisol reactions to stress could not be accounted for by: stress task performance, subjective task performance, eating disorders, menstrual cycle phase, oral contraceptive use, age, body mass index (BMI), or baseline cardiovascular or cortisol values. There

were no differences between groups in systolic blood pressure (SBP) or diastolic blood pressure (DBP) reactions to stress.

Responses to stress and disordered eating

Chapter 3 compared cardiovascular and cortisol reactions to an acute psychological stress task in 12 participants with evidence of disordered eating, symptoms of bulimia, and 12 healthy controls. Individuals with disordered eating showed blunted HR, stroke volume (SV), cardiac output (CO), and cortisol stress reactions compared to controls, as well as attenuated vasodilatory stress reactivity. There were no group differences in SBP and DBP reactivity. Given that the study reported in Chapter 2 provided evidence of blunted stress reactivity in women with exercise dependence and that exercise dependence is often co-morbid with disordered eating (Davis et al., 1995; 1997; Bamber et al., 2000), re-analyses were conducted adjusting for symptoms of exercise dependence as evidenced by scores on the Exercise Attitudes and Beliefs Questionnaire (EABQ). All group \times time interactions, indicative of group differences in reactivity, remained statistically significant after adjusting for EABQ scores. Additionally, the reactivity effects could not be attributed to group differences in stress task performance, subjective task impact or task engagement, menstrual cycle phase, oral contraception use, neuroticism, age, BMI, or estimated cardio-respiratory fitness.

Stress reactivity and cognitive ability

Chapters 4, 5, and 6 examined the associations between cognitive ability and cardiovascular reactivity, retrospectively, cross-sectionally, and prospectively using data from two large cohort studies. In Chapter 4, low cognitive ability, as indexed by relatively poor Alice Heim-4 (AH-4) scores, a measure of verbal and mathematical reasoning, and slow reaction times, was associated with relatively low HR and SBP reactivity to the paced

auditory serial arithmetic test (PASAT) seven years later. Only the association with HR reactivity survived full statistical adjustment, for sex, social economic status (SES), BMI, use of antihypertensive medication, and stress task performance. There were no significant associations between DBP reactivity and AH-4 score or simple reaction time. Post-hoc analyses of tertiles of cognitive ability indicated that those in the bottom third in AH-4 scores and in the slowest third of reaction time had the lowest HR reactivity.

Chapter 5 examined the cross-sectional association between cardiovascular and cortisol stress reactivity and cognitive ability, as indexed by scores on the AH-4 and by two memory tasks: immediate and delayed recall. Low SBP, DBP, HR, and area under the curve (AUC) cortisol reactions to acute stress were associated with low AH-4 test scores and poorer performance on the two memory tasks. Analyses of tertiles of AH-4 and memory task scores indicated a positive dose-response relationship between cognitive ability and cardiovascular and AUC cortisol reactivity. The associations remained statistically significant in regression models that adjusted for age, sex, SES, educational level, BMI, alcohol consumption, smoking, use of antihypertensive medication, use of antidepressant or anxiolytic medication, stress task commitment, and baseline cardiovascular/cortisol values.

Chapter 6 demonstrated that blunted HR reactions to acute stress were associated with low AH-4 test scores and longer choice reaction times (CRTs) five and 12 years later. SBP and DBP reactivity were not associated with cognitive ability at either time point. Post hoc analyses of tertiles of HR reactivity indicated a dose-response relationship between HR reactivity and AH-4 scores and CRT at both follow-ups; blunted HR reactivity was positively associated with poorer future cognitive ability. These associations remained statistically significant in regression models that adjusted for age cohort, sex, SES, disability status, depressive symptomatology, BMI, and baseline HR. HR reactivity was also associated with change in cognitive ability over time, i.e., low HR

reactivity was associated with poorer AH-4 scores and slower CRTs at the 12 year follow-up even after statistical adjustment for cognitive ability at the fourth follow-up, seven years earlier, i.e., blunted HR reactivity was positively associated with cognitive decline. The strongest association between HR reactivity and cognitive decline was observed in the oldest of the three cohorts of participants, who were 63 at the time of stress testing.

Extreme high and low cardiovascular stress responders and brain activation during stress

Chapter 7 confirmed the temporal stability of extreme stress responses and examined the neural activation differences in selected extreme exaggerated and blunted cardiac reactors to an interference stress task. Over four testing sessions, the exaggerated reactors, although showing some adaption of response over sessions, remained high reactors throughout; the blunted reactors continued to show little or no cardiac stress reactivity. During the fMRI laboratory session, exaggerated reactors showed a significant increase in HR from resting baseline to the control congruent task, and particularly to the stress incongruent task. The HRs of blunted reactors did not change significantly throughout the session. Blunted cardiac reactors showed decreased activation in the amygdala during the stress condition compared to the control condition. Exaggerated cardiac reactors showed increased activation in the brain stem, caudate, and cerebellum during the stress condition compared to the control condition. Additionally, there were significant group (exaggerated, blunted) differences in the anterior mid cingulate cortex (aMCC) activation, the exaggerated reactors showing significantly greater activation than the blunted reactors during the stress condition compared to the control condition. There were no group differences in subjective measures of performance, difficulty, engagement, how stressful participants found the task, nor on how stressful they found the scanner. Further, the neural activation effects could not be attributed to group differences in age or BMI.

Implications

The reactivity hypothesis (Obrist, 1981) has inspired thousands of studies over the past thirty years. The main focus, however, has been on conditions that give rise to exaggerated cardiovascular reactions to acute stress and the implications that exaggerated reactions hold for future cardiovascular health (Chida & Steptoe, 2010; Carroll, 2011). Until relatively recently blunted cardiovascular reactivity to acute psychological stress has, by implication, been regarded as benign or even protective (Carroll et al., 2009). However, over the past five years research emerging from two distinct fields: biological psychology and clinical psychology have begun to focus on the implications and correlates of the failure to react biologically to acute psychological stress (e.g. Pesonen et al., 2011; Kaess et al., 2011, Lovallo, 2011) and the relationship between previous traumatic experiences and blunted reactivity (Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012; Carpenter, Shattuck, Tyrka, Geraciotti, & Price, 2011). Although each field seemingly appears to be unaware of the other, both are engaging in similar research measuring biological reactions to acute stress and arriving at similar conclusions: that not biologically responding to stress is associated with a variety of negative health outcomes and behaviours. This thesis is timely and its findings resonate with the results emerging from a range of disparate stress research endeavours. While the presented thesis is primarily rooted in the field of biological psychology, it takes into account clinical psychology aspects (Chapters 2 & 3) and acknowledges the stress research being conducted across both disciplines. Table 8.1 provides a summary of clinical and biological psychology studies published since 2010 examining or showing blunted cardiovascular reactions to stress.

Table 8.1. Summary of clinical and biological psychology studies published since 2010 examining or showing blunted cardiovascular reactions to stress.

Author	Participants	Stress task used	Covariates	Results
Ginty & Conklin, 2011	N = 100 Mean (SD) age years = 19.6 (1.3) 62% female	Serial subtraction task	There were no group differences in: sex, age, anxiety, baseline cardiovascular activity	Individuals who perceive their lives as more stressful than their reported stress exposure would suggest (high PSDS) showed blunted HR reactivity relative to individuals who perceive their lives as less stressful than their reported stress exposure would suggest and those with moderate PSDS scores.
Phillips, Der, Shipton, & Benzeval, 2011	N = 852 Mean (SD) age years = 51.0 (9.39) 54% female	PASAT	Baseline cardiovascular level, age, sex, SES, antihypertensive medication status, smoking status, BMI, PASAT performance, earlier disability score, and depressive symptoms	HR reactivity to stress was associated with change in physical disability over time: those with lower HR reactions to stress were more likely to deteriorate over a 5 year period.
Allen, Bocek, & Burch, 2011	N = 149 Mean (SD) age years: Males = 20.3 (3.7) Females: 19.3 (2.0) 56% female	Serial subtraction task	Baseline cardiovascular levels	Those who had more psychological distress on the GHQ had lower SBP reactions to stress. Individuals with higher scores on the PSS had lower DBP reactivity. Women with higher levels of psychological distress had lower DBP reactivity than those with lower levels of psychological distress. Women with higher scores on the PSS and with higher psychological distress cores on the GHQ had lower levels of HR reactivity than those with low levels of stress.

Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012	N = 354 Mean (SD) age years: Men 0 adverse life events = 23.5 (0.3) Men 1 adverse life event = 23.7 (0.5) Men > 1 adverse life event = 24.6 (0.7) Women 0 adverse life events = 23.1 (0.3) Women 1 adverse life event = 23.5 (0.4) Women >1 adverse life event = 24.6 (0.5) 55% female	Speech task, 15-min mental arithmetic task	SES, cortisol diurnal cycle, subjective stress experience	Those who experience more adverse life events before the age of 15 have smaller HR and cortisol responses to stress.
Carroll, Bibbey, Roseboom, Phillips, Ginty, & de Rooij, 2012	N = 435 Mean (SD) age years = 58.3 (0.90) 51% female	Speech task, stroop task, mirror tracing	Baseline physiological activity appropriate to the dependent variable, sex, SES< weight, smoking, and stress task commitment	Low forced expiratory volume was associated with blunted HR and cortisol reactions to stress.
Carpenter, Shattuck, Tyrka, Geraciotti, & Price, 2011	N = 110 Mean (SD) age years: Physical abuse (N = 20) = 36.5 (12.5) No physical abuse (N = 90) = 29.1 (10.4) 100% female	TSST	Estrogen use, age, SES, perceived stress, depressive and anxiety symptoms, current or lifetime Axis I diagnosis, and other types of maltreatment.	Women with a history of physical abuse displayed blunted cortisol responses to a stress task.
Howard, Hughes, & James, 2011	N = 89 Mean (SD) age years = 19.70 (1.87) 100% female	Mental arithmetic task (subtraction problems)	None listed	Individuals with Type D personality disorder displayed significantly lower HR and cortisol and attenuated vasodilatory reaction to acute psychological stress compared to non-Type D individuals. Regression analyses showed an inverse relationship between the two Type D subscales and HR and CO and a positive relationship between the subscales and

				TPR.
Ouellet-Morin, Odgers, Danese, Bowes, Shakoor, Papadopoulos, Caspi, Moffitt, & Arseneault, 2011	N = 190 (maltreated/bullied N = 64; control = 126) 12-year-old children 49.5% female	Speech task, Children's PASAT	There were no differences between groups on: sex, birth weight, IQ, social problems, SES, BMI, pubertal maturity, perceived stress of the stress tasks, increased negative affect related to the stress tasks	Children who were maltreated/bullied had lower cortisol responses to the stress tasks. Among children who were maltreated/bullied lower cortisol responses were associated with more social and behavioural problems.
Pesonen, Kajantie, Jones, Pyhala, Lahti, Heinonen, Eriksson, Strandberg, & Raikonen, 2011	N = 272 M (SD) age years = 8.1 (0.3) 47% female	Trier Social Stress Test for Children	Time of day of baseline measurements, BMI, SES, quantity of glycyrrhizin in the licorice mothers consumed during pregnancy, mother-rated ODD/CD and anxiety symptoms	Children with ADHD-I behavioural symptoms displayed blunted cortisol responses compared with children without ADHD-I symptoms.
Kaess, Hille, Parzer, Maser-Gluth, Resch, & Brunner, 2011	N = 28 Mean (SD) age years: Patients who engaged in nonsuicidal self-injury (N = 14) = 16.6 (1.7) Healthy control subjects (N = 14) = 16.3 (2.2)	TSST	Psychological symptoms, negative affect, and dissociative experiences	The nonsuicidal self-injury group displayed a blunted cortisol response to the acute psychological stress task. There were no differences between groups in HR.
Hirvikoski, Olsson, Nordenstrom, Lindholm, Nordstrom, & Lajic, 2011	N = 60 Mean (SD) age years: ADHD participants (N = 30) = 33.3 (8.2) Controls (N = 30) = 32.6 (10.1) 35% female	PASAT	Beck Depression Inventory scores, Beck Anxiety Inventory scores. There were no differences between groups in: age, sex, IQ, medical treatment, nicotine abuse, or general hypoarousal.	The ADHD group showed significantly lower cardiovascular responses to stress compared to the control group.
Luecken & Roubinov, 2012	N = 75 Mean (SD) age years = 18.9 (1.0) 50% female	Role-playing task (challenging social situation)	Sex, BMI, anxiety	Those with more negative family relationships in childhood displayed attenuated HR reactivity to the task.

Brenner & Beauchaine, 2011	N = 206 Mean (SD) age years = 9.9 (1.5) 35% female	Monetary-incentive task	Age	Lower PEP reactivity to the stress task prospectively predicted increases in alcohol use over a three year period.
de Vries-Bouw, Popma, Vermeiren, Doreleijers, Van de Ven, & Jansen, 2011	N = 68 Mean (SD) age years = 13.9 (0.8) 100% male	Speech task	None	Lower HR and higher HRV reactions to acute psychological stress predicted a higher reoffending rate among delinquent adolescents.

Motivational dysregulation and blunted cardiovascular and cortisol reactions to stress

It has previously been proposed that blunted physiological stress reactivity may be a marker of central motivational dysregulation (Carroll et al., 2009; Carroll, Phillips, & Lovallo, 2011), a suboptimal functioning of the physiological systems in the brain that support motivation and motivated behaviour. One of the main aims of this thesis was to further test this theory. This was achieved using a three pronged approach: 1) investigating physiological responses to stress in populations that would appear to show motivational dysregulation (Chapters 2 and 3) to determine whether they too have blunted reactivity, 2) gaining a clearer understanding of the relationship between cognitive ability and physiological responses to acute stress using cognitive tasks that are independent of the laboratory stress task (Chapters 4, 5, & 6), and 3) examining neural activation, using fMRI, during acute stress in exaggerated and blunted cardiac reactors identified by exhaustive pre-screening (Chapter 7). The results, earlier described, from these studies provide supportive evidence for the notion that blunted physiological responses to acute psychological stress could be a marker of central motivational dysregulation, a disengagement in the motivational areas of the brain when the individual is faced with an acute challenge. Support comes from the evidence provided in this thesis that blunted physiological responses to acute stress are associated with a non-substance abuse addiction and a disorder, bulimia, related to hypo-functioning of the brain in response to reward (Bohon & Stice, 2011). It is widely accepted that cognitive performance requires the integrity of motivational systems (Busato, Prins, Elshout, & Hamaker, 2000; Dweck, 1986; McClelland, Atkinson, Clark, & Lowell, 1953; Pintrich & Schunk, 1986) and results from three studies in this thesis revealed that poor cognitive performance was associated with blunted physiological reactions to stress which further adds to the argument of some sort

of dysregulation in the motivational systems of individuals with blunted responses to stress. Perhaps the most compelling evidence of motivational dysregulation comes from the final study of this thesis which shows a hypo-activation during stress in blunted reactors compared to exaggerated reactors in the anterior mid-cingulate cortex: an area of the brain associated with motivation, high cognitive functioning, engagement, and emotional control, and a deactivation during stress compared to rest in the amygdala and frontal cortex: areas of the brain associated with motivation and emotion. It is important to note that in the studies that included subjective measures of stress task engagement, difficulty, and stressfulness, blunted reactors did not differ from those with average or exaggerated reactivity. In the epidemiological analyses reported here, the associations between blunted reactivity and cognitive ability were still evident after mainly adjusting for task performance or subjective task involvement. It would appear that individuals showing blunted stress reactivity “feel” the same as those with larger reactions. It is not simply a matter of failing to engage with the stress tasks. Something more nuanced would seem to be occurring, i.e., subjective engagement and involvement is apparently preserved. It is simply that some individuals do not react biologically to acute stress exposures. Chapter 7 enables us to see what is happening in areas of the brain and further confirms a dysregulation occurring in areas associated with motivation and emotion. As indicated, individuals with blunted reactivity report being just as engaged in the tasks as other responders and their performance scores are not significantly different. Nevertheless, areas of the brain associated with motivation are not activated when challenged by a stress task. Individuals with blunted reactivity also report feeling just as stressed during the task as exaggerated reactors, yet they experience a decrease in activation in areas of the brain that process stressful, threatening, and challenging stimuli. There is a dysregulation or disengagement occurring between the conscious and unconscious in those with blunted

reactions. They are feeling one thing, but their biology is not reacting to those feelings experiences in the brain, sympathetic system, or the hypothalamic-pituitary-adrenal (HPA) axis. It would appear, then, that a dysregulation is occurring in the motivational areas of the brain that is influencing these other systems, as well as influencing health, behaviour, and cognitive ability.

Reward Deficiency Syndrome (RDS)

Reward Deficiency Syndrome (RDS) is a relatively recent concept that shares much with the notion of central motivational dysregulation. RDS is hypothesised to arise from hypo-activation in the reward (limbic) circuits in the brain (Blum et al., 2011; Blum, Gardner, Oscar-Berman, & Gold, 2012; Blum et al., 1995). The syndrome is proposed to be based on a common genetic deficiency in the dopamine D2 receptor. RDS can manifest in many different ways (Blum et al., 2011); it has been related to addictive behaviours such as alcoholism, smoking; to adiposity and obesity; impulsive behaviours such as attention-deficit disorder; compulsive behaviours such as pathological gambling and bulimia; and personality disorders such as conduct disorder and anti-social personality disorder (Blum et al., 1995). It was originally proposed and later confirmed that RDS was associated with a dysregulation of areas of the brain associated with reward and that the deficit in the brain causes low levels of important chemicals in the body (e.g. serotonin and dopamine) which contributes to the maintenance of the disorders (Blum et al., 2011). Much of the focus of research on RDS has been on how people with RDS, and the disorders associated with it, respond to rewarding stimuli (Andrews et al., 2011; Bjork, Smith, & Hommer, 2008; Reuter et al., 2005; Stark et al., 2011; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008; Wilbertz et al., 2012), but scant research has been conducted on how individuals with RDS respond to acute stress. This is somewhat surprising given that increases in stress are associated with higher use of the unhealthy substances (e.g. alcohol, high fat foods) often

used to increase feelings of satisfaction (Blum et al., 1995; 2011). It should be noted, as previously mentioned in the General Introduction and earlier in this chapter, that stress reactions in certain disorders associated with RDS have been examined (i.e., alcohol dependence), but there appear to be no published studies examining the relationship between RDS *per se* and biological reactions to stress. However, given the similarity of disorders associated with RDS and disorders associated with blunted reactivity, it is reasonable to propose that blunted physiological reactions to acute stress may be a marker for RDS and/or individuals with RDS are more than likely exhibit blunted physiological reactions to acute psychological stress. Chapter two demonstrates that a non-substance abuse addiction, exercise dependence, is associated with blunted physiological responses to stress and Chapter three demonstrates that a compulsive and detrimental disorder, bulimia, is also associated with blunted stress responses. Both addiction and compulsive behaviours are characteristic in RDS. Research has shown alcoholism, obesity, conduct disorder, smoking, and pathological gambling to be related to blunted cardiovascular and/or cortisol stress reactivity; all of them are also associated with RDS. Chapter seven revealed hypo-activation of the amygdale and other areas of the limbic system during a stressful stimulus in blunted cardiac reactors: dysregulation of these areas of the brain during reward is related to RDS. Figure 8.1 proposes a model showing the possible relationship between RDS and blunted physiological reactions to stress using the information gained from this thesis.

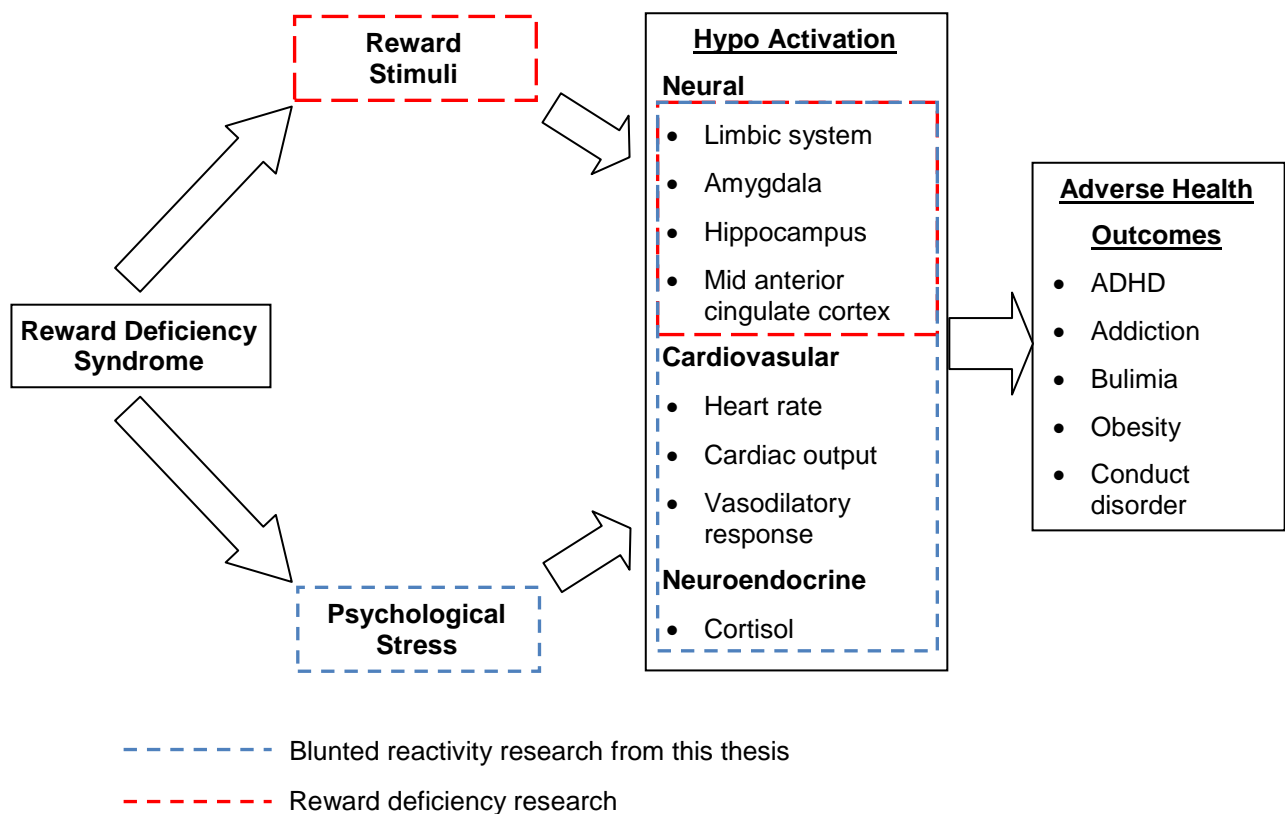


Figure 8.1. A model showing the role psychological stress and physiological responses to psychological stress may play in RDS using information gained from this thesis.

Limitations

The present thesis is not without limitations. Individual limitations regarding each study have been discussed in-depth in the Discussion sections of each of the empirical chapters and therefore this section focuses on the general limitations of the thesis as a whole. The small sample sizes tested in the laboratory studies could be regarded as a limitation.

However, these samples were extremes drawn for surveys or from testing of much larger samples: in each case the goal was to isolate the most extreme groups for laboratory testing. During each of the screening stages a large number of participants were surveyed (Chapter 2: N = 219 and Chapter 3: N = 455) and then the most extreme cases selected.

The number of participants tested in the fMRI study could also be regarded as modest, but

90 potential participants were screened in full cardiovascular stress laboratory protocols and additional participants were identified from a colleague's stress testing sessions as part of an immune reactivity project, so the individuals tested in the fMRI truly represented the most extreme cardiovascular stress reactors. Additionally, the number of participants in the fMRI study is in line with previous studies of this nature (Gianaros, May, Siegle, & Jennings, 2005). Another limitation is that the findings for blunted reactivity do not always emerge for all measures of cardiovascular reactivity, and in several instances BP reactions to stress were not related to the outcomes. A probable explanation for this is the substantial influence sympathetic activation, specifically β -adrenergic drive, has on individual differences in reactions to stress. β -adrenergic antagonists have been shown to attenuate cardiac, but not BP, reactions to acute stress exposure (Sherwood et al., 1986; Winzer et al., 1999) and greater β -adrenergic activation has explained differences between exaggerated and lower cardiac reactors (Balanos et al., 2010). It is worth noting that in all of my studies in which blunted cortisol reactivity was related to the outcome, blunted HR reactivity was also related. This is perhaps not surprising when one considers that cortisol reactivity is more strongly related to HR reactivity than to BP reactivity (Bosch et al., 2009). Then there are issues about generalisation. Chapters 2 and 3 only tested female participants; however, both exercise dependence and disordered eating are decidedly more prevalent in female populations (Anderson, 1995; Bamber et al., 2000; Bamber, Cockerill, Rodgers, & Carroll, 2003; Woodside, 2001). Chapter 7 only tested male participants; however, there is no compelling reason for suspecting that women would not exhibit temporal stability across testing sessions (Carroll, Turner, Lee, & Stephenson, 1984) or that there would be gender differences in neural activation to stress (Gianaros et al., 2005). Finally, it remains possible that the findings could, to an extent, arise from confounding by

some unmeasured or poorly measured variable (Christenfeld, Sloan, Carroll, & Greenland, 2004); however, all studies adjusted for numerous potential confounders.

Strengths

There are also a number of strengths to this thesis. Firstly, it included a combination of laboratory work and secondary analyses of large data sets, providing the opportunity to investigate prospective and retrospective, as well as cross-sectional, relationships and allowing for substantial adjustment for possible confounding variables. The secondary analyses use data from two large and respected epidemiological data sets, The West of Scotland Twenty-07 Study and the Dutch Famine Birth Cohort Study. Having similar results from completely independent and unique populations using independent and unique stress tests further strengthens the findings. Additionally, participants of all ages were tested. Young participants were tested in the laboratory studies (Chapter 2, Chapter 3, and Chapter 7), middle aged participants were tested in the cross-sectional study (Chapter 5), older participants were tested in the retrospective study (Chapter 4), and a diverse age range across populations was tested in the prospective study (Chapter 6). Finally, and perhaps the biggest strength, is the use of a variety of objective measures to measure biological responses to stress: standard blood pressure cuff (Chapters 2-7), portapres (Chapter 5), electrocardiography (Chapters 3, 7), Doppler echocardiography (Chapters 3, 7), pulse oximeter (Chapter 7), cortisol (Chapters 2, 3, 5), and fMRI (Chapter 7). The use of a sophisticated non-invasive measure, such as Doppler echocardiography, is rare in the field of cardiovascular psychophysiology, reliant as it often is on simple intermittent measures of blood pressure and pulse rate. Doppler echocardiography is a more reliable, accurate, and clinically acceptable and accurate measure of cardiac activity during a haemodynamic challenge when compared with other measures, such as pulse rate and cardiac output derived from impedance cardiography (Fellahi, Caille, Charron,

Deschamps-Berger, & Vieillard-Baron, 2009). The sensitivity of echocardiography was especially helpful in confirming the temporal stability of extreme reactions to stress and for teasing out some of the conflicting data regarding disordered eating and reactions to stress (Messerli-Burgy et al., 2010; Koo-Loeb et al., 1998). The combination of cardiovascular and cortisol responses to acute stress (Chapter 2, 3, 5) provides an assessment of both branches of the stress effector system: the HPA axis and the sympathetic nervous system. A study that combines both Doppler echocardiography and fMRI (Chapter 7) to measure responses to acute psychological stress is unique. The combination of using non-invasive yet sensitive measures in a cohort of extreme reactors can provide important insights to the levels of the system that may contribute to individual differences in stress reactivity. Lovallo (2005) proposes a three level response system in which Level I includes the motivational and emotional responses of the brain, cognitive processes, and appraisals, Level II incorporates the brainstem, hypothalamus, and limbic system as pathways to communicate with the body and influence endocrine responses, the area between Level II and Level III takes into account autonomic and endocrine outputs to the periphery and Level III incorporates the peripheral tissues and existing structures of the body. Chapters 2, 3, & 5 provide further information on the area between Level II and Level III by examining cortisol (endocrine) responses to stress. Chapter 7 directly tests differences in Levels II and Level III by measuring BOLD activation responses to stress in the whole brain. Chapters 2-7 test for differences in Level I by giving self-report measures after testing asking for appraisals on stressfulness and engagement. As a whole, nearly all levels and connection between levels of Lovallo's model are explored in this thesis.

Future Directions

There are a number of ways future research could build upon the work presented in this thesis; a few will be highlighted in this section. Future research should focus on further

testing of whether blunted physiological reactions to acute psychological stress are a marker of risky behaviour, addiction, and poor health. The present thesis demonstrates the relationship between blunted reactivity and unhealthy behaviours, but does not demonstrate if blunted reactivity predicts future risky and addictive behaviours. A possible way to test this is to test a population just before a key transitional period in their lives that may increase stress levels and that has been related to the uptake of negative health behaviours. For example, the move from high school to university is considered a challenging and stressful transition (Blimings & Miltenberg, 1981; Raymore, Barber, & Eccles, 2001). The changes bring a sense of unfamiliarity at a stage of development when the individual is establishing, refining, and testing new identities and searching for a sense of security (Blimlings & Miltenberg, 1981; Scheier & Botvin, 1997; Rosen, Compas, & Tacy, 1993). Although some individuals easily adapt during this period, others struggle (Blimling & Miltenberg, 1981) and begin or increase maladaptive risky behaviours as a coping mechanism. Evidence indicates that the move from high school to university can be associated with smoking uptake (McDermott, Dobson, & Russell, 2004), binge drinking (Borsari, Murphy, & Barnett, 2007; Ham & Hope, 2003), disordered eating (Ackard, Croll, & Kearney-Cooke, 2002; Vohs, Heatherton, & Herrin, 2001), weight gain (Levitsky, Halbmaier, & Mrdjenovic, 2004; Provencher et al., 2009), increased risk taking (Kelley, Schochet, & Landry, 2004), and depression (Dyson & Renk, 2006). Many of these behaviours and states are associated with blunted stress reactivity. If individuals underwent a standardised laboratory stress testing protocol before this period and followed up throughout their first year of university the relationship between blunted reactivity and uptake or increase of these unhealthy behaviours could be tested. This longitudinal design would provide a way to understand if blunted reactivity is a risk marker for these behaviours.

Future research could usefully incorporate measures of neurotransmitters, such as dopamine, serotonin, and norepinephrine. These neurotransmitters are related to the functioning of areas of the brain that appear to show a dysregulation in response to stress (Chapter 7) and dopamine and serotonin deficiencies have been related to RDS and other manifestations of motivational dysregulation (Blum et al., 2000; Rothman, Blough, & Baumann, 2007; Treadway et al., 2012). A dysregulation in the norepinephrine stress response has been shown in women with bulimia (Koo-Loeb et al., 1998; Pirke et al., 1992). Further, these neurotransmitters play an important role in the central feedback subsystem which is a vital part of the Level II responses discussed earlier (Lovallo, 2005).

Finally, studying the association between certain genetic polymorphisms and blunted/exaggerated cardiovascular and cortisol reactions stress may help better understand the extent to which blunted stress reactivity is determined by genetic, environmental, or genetic \times environmental influences. There are a few candidate genes which could possibly be related to blunted stress reactivity. The D2, dopamine receptor gene, should be of primary interest given its relationship to RDS (Blum et al., 2011) and the possible connection between RDS and blunted cardiovascular reactivity. A second gene is the serotonin transporter (5HTT) gene which has been associated with depression (Lesch et al., 1996; Caspi et al., 2003), higher cardiovascular reactions to acute psychological stress (Williams et al., 2001; 2008), and bulimia (Akkermann et al., 2012). A third gene is the variable number tandem repeat (VNTR) polymorphism of the MAOA gene, which has been related to an interaction between early life stress and imprisonment (Caspi et al., 2002) and impulsivity (Manuck et al., 2000; Manuck, Flory, Muldoon, & Ferrell, 2002). A fourth gene is a polymorphism of the COMT gene which has been implicated in individual differences in emotional and physiological responsivity (Goldman, Oroszi, & Ducci, 2005; Smolka et al., 2005; Zubieta et al., 2003), as well as

and proness to addiction (Enoch, Waheed, Harris, Alabaugh, & Goldman, 2006; Vandenberg, Rodriguez, Miller, Uhl, & Lachman, 1997).

Conclusions

In conclusion, this thesis used a mixed methods approach of laboratory testing and secondary analyses to further investigate the notion that blunted physiological reactions to acute psychological stress may be indicative of numerous negative health outcomes and behaviours. It was confirmed that blunted reactivity is associated with non-substance dependence disorders such as exercise dependence and maladaptive health behaviours such as disordered eating. It was also confirmed that lower cognitive ability was associated with blunted reactivity, and that blunted reactivity could predict cognitive decline over a 7 year period. Finally, it was shown that there are brain activation differences between extreme high and extreme low cardiac stress reactors during an acute stress exposure. Individuals with blunted cardiac reactions to stress showed hypo-activation in the limbic areas of their brain associated with motivation and emotion. This thesis provides further evidence that blunted cardiovascular reactions to stress are associated with a number of adverse outcomes. Given the information presented here and current research in the field, along with 30 years of research examining exaggerated reactivity to stress it is perhaps fitting to now conclude that both blunted and exaggerated reactivity might be properly considered to be maladaptive.

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Appendix 1: Exercise Attitudes and Beliefs Questionnaire

Below are a number of statements about attitudes to exercise and exercise behaviour.

Please indicate the extent to which these statements are in line with your attitudes and behaviour, by circling the appropriate number between 0 (definitely not) and 6 (definitely yes) for each statement.

	Definitely not						Definitely yes
1. I am constantly thinking about exercise	0	1	2	3	4	5	6
2. I prioritise exercise above all other social activities	0	1	2	3	4	5	6
3. I sometimes continue to exercise against medical advice	0	1	2	3	4	5	6
4. I have lost friends because of my commitment to exercise	0	1	2	3	4	5	6
5. It is very important to me that I keep to a strict exercise regime	0	1	2	3	4	5	6
6. I feel bad when I have to interrupt my exercise schedule	0	1	2	3	4	5	6
7. I find the thought that I may not be able to exercise as a result of injury depressing	0	1	2	3	4	5	6
8. When I have tried to reduce the amount I exercise I have generally been unsuccessful	0	1	2	3	4	5	6
9. I worry that I am having to exercise more and more to get the same 'buzz'	0	1	2	3	4	5	6
10. Exercise does not make me feel good, but not exercising makes me feel worse	0	1	2	3	4	5	6
11. Most of the time I exercise alone	0	1	2	3	4	5	6
12. I often underestimate to others the amount of time I spend exercising	0	1	2	3	4	5	6